PYRIDINE DERIVATIVES AND USE THEREOF AS UROTENSIN II ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel 4-(piperidinyl- and pyrrolidinyl-alkyl-ureido)-pyridine derivatives of the General Formula 1 and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the General Formula 1 and especially their use as neurohormonal antagonists.

BACKGROUND OF THE INVENTION

Urotensin II is a cyclic 11-amino acid peptide neurohormone considered to be the most potent vasoconstrictor known, up to 28-fold more potent than endothelin-1. The effects of urotensin II are mediated through activation of a G-protein coupled receptor, the UT receptor, also known as GPR14 or SENR (Ames RS, et al, "Human urotensin-II is a potent vasoconstrictor and agonist for the orphan receptor GPR14" Nature (1999) 401, 282-6. Mori M, Sugo T, Abe M, Shimomura Y, Kurihara M, Kitada C, Kikuchi K, Shintani Y, Kurokawa T, Onda H, Nishimura O, Fujino M. "Urotensin II is the endogenous ligand of a G-protein-coupled orphan receptor, SENR (GPR14)" Biochem. Biophys. Res. Commun. (1999) 265,123-9. Liu Q, Pong SS, Zeng Z, et al, "Identification of urotensin II as the endogenous ligand for the orphan G-protein-coupled receptor GPR14" Biochem. Biophys. Res. Commun. (1999) 266, 174-178) Urotensin II and its receptor are conserved across evolutionarily distant species, suggesting an important physiological role for the system (Bern HA, Pearson D, Larson BA, Nishioka RS. "Neurohormones from fish tails: the caudal neurosecretory system. I. Urophysiology and the caudal neurosecretory system of fishes" Recent Prog. Horm. Res. (1985) 41, 533-552). In euryhaline fish, urotensin II has an osmoregulatory role, and in mammals urotensin II exerts potent and complex hemodynamic actions. The response to urotensin II is dependent on the anatomical source and species of the tissue being

studied. (Douglas SA, Sulpizio AC, Piercy V, Sarau HM, Ames RS, Aiyar NV, Ohlstein EH, Willette RN. "Differential vasoconstrictor activity of human urotensin-II in vascular tissue isolated from the rat, mouse, dog, pig, marmoset and cynomolgus monkey" Br. J. Pharmacol. (2000) 131, 1262-1274. Douglas, SA, Ashton DJ, Sauermelch CF, Coatney RW, Ohlstein DH, Ruffolo MR, Ohlstein EH, Aiyar NV, Willette R "Human urotensin-II is a potent vasoactive peptide: pharmacological characterization in the rat, mouse, dog and primate" J. Cardiovasc. Pharmacol. (2000) 36, Suppl 1:S163-6).

Like other neurohormones, urotensin II has growth stimulating and profibrotic actions in addition to its vasoactive properties. Urotensin II increases smooth muscle cell proliferation, and stimulates collagen synthesis (Tzandis A, et al, "Urotensin II stimulates collagen synthesis by cardiac fibroblasts and hypertrophic signaling in cardiomyocytes via G(alpha)q- and Ras-dependent pathways" J. Am. Coll. Cardiol. (2001) 37, 164A. Zou Y, Nagai R, and Yamazaki T, "Urotensin II induces hypertrophic responses in cultured cardiomyocytes from neonatal rats" FEBS Lett (2001) 508, 57-60). Urotensin II regulates hormone release (Silvestre RA, et al, "Inhibition of insulin release by urotensin II-a study on the perfused rat pancreas" Horm Metab Res (2001) 33, 379-81). Urotensin II has direct actions on atrial and ventricular myocytes (Russell FD, Molenaar P, and O'Brien DM "Cardiostimulant effects of urotensin-II in human heart in vitro" Br. J. Pharmacol. (2001) 132, 5-9). Urotensin II is produced by cancer cell lines and its receptor is also expressed in these cells. (Takahashi K, et al, "Expression of urotensin II and urotensin II receptor mRNAs in various human tumor cell lines and secretion of urotensin II-like immunoreactivity by SW-13 adrenocortical carcinoma cells" Peptides (2001) 22, 1175-9; Takahashi K, et al, "Expression of urotensin II and its receptor in adrenal tumors and stimulation of proliferation of cultured tumor cells by urotensin II" Peptides (2003) 24, 301-306; Shenouda S, et al, "Localization of urotensin-II immunoreactivity in normal human kidneys and renal carcinoma" J Histochem Cytochem (2002) 50, 885-889). Urotensin II and its receptor are found in spinal cord and brain tissue, and intracerebroventricular infusion of urotensin II into mice induces behavioral changes (Gartlon J, et al, "Central effects of urotensin-II following ICV administration in rats" Psychopharmacology (Berlin) (2001) 155, 426-33).

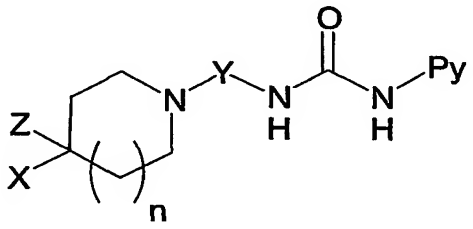
Dysregulation of urotensin II is associated with human disease. Elevated circulating levels of urotensin II are detected in hypertensive patients, in heart failure patients, in diabetic patients, and in patients awaiting kidney transplantation (Cheung, BM, et al., "Plasma concentration of urotensin II is raised in hypertension" J. Hypertens. (2004) 22, 1341-1344; Totsune K, et al, "Role of urotensin II in patients on dialysis" Lancet (2001) 358, 810-1; Totsune K, et al, "Increased plasma urotensin II levels in patients with diabetes mellitus" Clin Sci (2003) 104, 1-5; Heller J, et al, "Increased urotensin II plasma levels in patients with cirrhosis and portal hypertension" J Hepatol (2002) 37, 767-772).

Substances with the ability to block the actions of urotensin II are expected to prove useful in the treatment of various diseases. WO-2001/45694, WO-2002/78641, WO-2002/78707, WO-2002/79155, WO-2002/79188, WO-2002/89740, WO-2002/89785, WO-2002/89792, WO-2002/89793, WO-2002/90337, WO-2002/90348, WO-2002/90353, WO-2004/043366, WO-2004/043368, WO-2004/043369, WO-2004/043463, WO-2004/043917 and WO-2004/043948 disclose certain sulfonamides as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance. WO-2001/45700 and WO-2001/45711 disclose certain pyrrolidines or piperidines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. These derivatives are different from the compounds of the present invention as they do not comprise urea derivatives bearing a 4-pyridinyl-like moiety. WO-2002/047456 and WO-2002/47687 disclose certain 2-amino-quinolones as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2002/058702 discloses certain 2-amino-quinolines as urotensin II receptor antagonists and their use to treat diseases associated with a urotensin II imbalance. WO-2001/66143 discloses certain 2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-4-ylamine derivatives useful as urotensin II receptor antagonists, WO-2002/00606 discloses certain biphenyl compounds useful as urotensin II receptor antagonists, and WO-2002/02530 and WO-2004/073634 also disclose certain compounds useful as urotensin II receptor antagonists. WO-2002/076979 and WO-2003/048154 disclose certain quinoline derivatives as urotensin II receptor antagonists, and their use to treat diseases associated with a urotensin II imbalance.

EP 428434 discloses certain alkylureidopyridines as neurokinin and substance P antagonists. WO-99/21835 discloses certain ureidoquinolines as H+-ATPase and bone resorption inhibitors. WO-2001/009088 discloses certain substituted heteroarylureas as inhibitors of the CCR-3 receptor. All of these ureidopyridine derivatives differ in their composition from compounds of the present invention. The present invention comprises *N*-(cyclic amino alkyl)-*N'*-pyridin-4-yl urea derivatives which are novel compositions of matter and which are useful as urotensin II receptor antagonists.

DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the General Formula 1.



General Formula 1

wherein:

Py represents pyridin-4-yl which is disubstituted in positions 2 and 6, whereby the substituent in position 2 is C_{1-7}-alkyl, aryl-C_{1-7}-alkyl, or (*E*)-2-aryl-ethen-1-yl, and the substituent in position 6 is hydrogen or C_{1-7}-alkyl;

X represents aryl; aryl-C_{1-7}-alkyl-; aryl-O-; aryl-C_{1-7}-alkyl-O-; R^1-SO_2NR^2-; R^1-$CONR^2$-; aryl-R^8-$CONR^2$-; R^1-NR^3CONR^2-; R^1-NR^2CO-; or X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group;

Z represents hydrogen; in case X represents aryl or aryl-C_{1-7}-alkyl Z represents hydrogen, hydroxyl, carboxyl or R^4-NR^5CO-; in case X represents R^1-NR^2CO- Z represents hydrogen or C_{1-7}-alkyl; or in case X represents aryl or aryl-C_{1-7}-alkyl and n represents the number 0, Z represents hydrogen, hydroxyl, carboxyl, R^4-NR^5CO-, aryl or aryl-C_{1-7}-alkyl;

Y represents $-C(R^6)(R^7)(CH_2)_m-$ or $-(CH_2)_mC(R^6)(R^7)-$;

m represents the numbers 1 or 2;

n represents the numbers 0 or 1;

R^1 represents aryl or aryl-C_{1-7}-alkyl;

R^2 represents hydrogen; C_{1-7}-alkyl; 2-hydroxyethyl; aryl-C_{1-7}-alkyl; or a saturated carbocyclic ring;

R^3 represents hydrogen or C_{1-7}-alkyl;

R^4 represents hydrogen; C_{1-7}-alkyl; aryl; aryl-C_{1-7}-alkyl; or forms together with R^5 a saturated 4-, 5- or 6-membered ring including the nitrogen atom to which R^4 and R^5 are attached as ring atom;

R^5 represents hydrogen; C_{1-7}-alkyl; 2-hydroxyethyl; or forms together with R^4 a saturated 4-, 5- or 6-membered ring including the nitrogen atom to which R^4 and R^5 are attached as ring atom;

R^6 represents hydrogen; C_{1-7}-alkyl; aryl; aryl-C_{1-7}-alkyl; or forms together with R^7 a saturated carbocyclic ring including the carbon atom to which R^6 and R^7 are attached as ring atom;

R^7 represents hydrogen; methyl; or forms together with R^6 a saturated carbocyclic ring including the carbon atom to which R^6 and R^7 are attached as ring atom.

R^8 represents a saturated carbocyclic ring.

In a preferred embodiement also the following forms are encompassed: optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

The term 'aryl' means a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system, consisting of a five- or six- membered aromatic ring, or of a fused five-six or six-six aromatic ring system. Preferred aryl groups are for example 2-furyl; 2-thienyl; phenyl; 2-methylphenyl; 3-methylphenyl; 4-

methylphenyl; 2-biphenyl; 3-biphenyl; 4-biphenyl; 2-methoxyphenyl; 3-methoxyphenyl; 4-methoxyphenyl; 3,4-dimethoxyphenyl; 2,6-dimethoxyphenyl; 2,5-dimethoxyphenyl; 2-phenoxyphenyl; 3-phenoxyphenyl; 4-phenoxyphenyl; 2-cyanophenyl; 3-cyanophenyl; 4-cyanophenyl; 2-fluorophenyl; 3-fluorophenyl; 4-fluorophenyl; 2,4-difluorophenyl; 2,5-difluorophenyl; 2,6-difluorophenyl; 3,4-difluorophenyl; 2-chlorophenyl; 3-chlorophenyl; 4-chlorophenyl; 3,4-dichlorophenyl; 2-bromophenyl; 3-bromophenyl; 4-bromophenyl; 2-trifluoromethylphenyl; 3-trifluoromethylphenyl; 4-trifluoromethylphenyl; 3,5-bis-trifluoromethylphenyl; 4-trifluoromethoxyphenyl; 4-ethylphenyl; 4-n-propylphenyl; 2-*iso*-propylphenyl; 4-*iso*-propylphenyl; 4-*tert*-butylphenyl; 4-n-pentylphenyl; 4-bromo-2-ethylphenyl; 2-methanesulfonylphenyl; 3-methanesulfonylphenyl; 4-methanesulfonylphenyl; 4-acetamidophenyl; 4-hydroxyphenyl; 4-*iso*-propyloxyphenyl;4-n-butoxyphenyl; 2-methoxy-4-methylphenyl; 4-methoxy-2,3,6-trimethylphenyl; 5-bromo-2-methoxy-phenyl; 2-pyridyl; 3-pyridyl; 4-pyridyl; 1-naphthyl; 2-naphthyl; 4-(pyrrol-1-yl)phenyl; 4-benzoylphenyl; 5-dimethylaminonaphth-1-yl; 5-chloro-3-methylthiophen-2-yl; 5-chloro-3-methyl-benzo[b]thiophen-2-yl; 3-(phenylsulfonyl)-thiophen-2-yl; 2-chloro-thien-5-yl; 2,5-dichloro-thien-3-yl; 4,5-dichlorothien-2-yl; 2-(2,2,2-trifluoroacetyl)-1-2,3,4-tetrahydroisoquinolin-7-yl; 4-(3-chloro-2-cyanophenyloxy)phenyl; 2-(5-benzamidomethyl)thiophenyl; 5-quinolyl-; 6-quinolyl; 7-quinolyl; 8-quinolyl; (2-acetylamino-4-methyl)thiazol-5-yl; or 1-methylimidazol-4-yl. For the substituents X, R^4 and R^6 aryl means preferably phenyl or phenyl mono- or disubstituted independently with C_{1-7}-alkyl, C_{1-7}-alkyl-O-, trifluoromethyl or halogen. For the substituent x aryl means preferably phenyl or phenyl mono- or disubstituted independently with C_{1-7}-alkyl, C_{1-7}-alkyl-O-, trifluoromethyl or halogen.

The term 'C_{1-7}-alkyl' means straight or branched chain groups with one to seven carbon atoms such as methyl, ethyl, n-propyl, 3-allyl, *iso*-propyl, n-butyl, *iso*-butyl, tert.-butyl, n-pentyl, iso-pentyl, n-hexyl and n-heptyl; preferably one to four carbon atoms. Preferred examples of C_{1-7}-alkyl groups are methyl, ethyl and n-propyl. Most preferred examples of C_{1-7}-alkyl groups are methyl and ethyl.

The term 'saturated carboxyclic ring' means a saturated cyclic alkyl group with three to six carbon atoms. Preferred examples of saturated carbocyclic rings are

cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. For the substituent R^8 'saturated carboxyclic ring' means preferably 1,1-cyclopropane-diyl.

The term 'aryl-C_{1-7}-alkyl' means a C_{1-7}-alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred examples of aryl-C_{1-7}-alkyl groups are 3-phenylpropyl, phenethyl, benzyl, and benzyl substituted in the phenyl ring with C_{1-7}-alkyl, C_{1-7}-alkyl-O-, trifluoromethyl or halogen such as 4-methylbenzyl, 3-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 3-methoxybenzyl, 2-methoxybenzyl, 4-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 2-trifluoromethylbenzyl, 4-chlorobenzyl, 3-chlorobenzyl, 2-chlorobenzyl, 4-fluorobenzyl, 3-fluorobenzyl, and 2-fluorobenzyl.

The term 'aryl-O-' means an aryl group as previously defined that is attached to an oxygen atom. Preferred examples of aryl-O- groups are phenoxy and phenoxy substituted in the phenyl ring with C_{1-7}-alkyl, C_{1-7}-alkyl-O-, trifluoromethyl or halogen such as 4-methylphenoxy, 4-methoxyphenoxy, 4-trifluoromethylphenoxy, 4-chlorophenoxy, 4-fluorophenoxy, 3-methylphenoxy, 3-methoxyphenoxy, 3-trifluoromethylphenoxy, 3-chlorophenoxy, 3-fluorophenoxy, 2-methylphenoxy, 2-methoxyphenoxy, 2-trifluoromethylphenoxy, 2-chlorophenoxy and 2-fluorophenoxy.

The term 'aryl-C_{1-7}-alkyl-O-' means a C_{1-7}-alkyl group as previously defined in which one hydrogen atom has been replaced by an oxygen atom and one additional hydrogen atom has been replaced by an aryl group as previously defined. Preferred examples of aryl-C_{1-7}-alkyl-O- groups are 3-phenylpropyloxy, 2-phenethyloxy, benzyloxy and benzyloxy substituted in the phenyl ring with C_{1-7}-alkyl, C_{1-7}-alkyl-O-, trifluoromethyl or halogen such as 4-methylbenzyloxy, 3-methylbenzyloxy, 2-methylbenzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 2-methoxybenzyloxy, 4-trifluoromethylbenzyloxy, 3-trifluoromethylbenzyloxy, 2-trifluoromethylbenzyloxy, 4-chlorobenzyloxy, 3-chlorobenzyloxy, 2-chlorobenzyloxy, 4-fluorobenzyloxy, 3-fluorobenzyloxy and 2-fluorobenzyloxy.

The term 'C_{1-7}-alkyl-O-' means a C_{1-7}-alkyl group as previously defined that is attached to an oxygen atom. Preferred examples of C_{1-7}-alkyl-O- groups are methoxy, ethoxy, n-propyloxy and *iso*-propyloxy.

The term '(*E*)-2-aryl-ethen-1-yl' means groups such as (*E*)-2-phenylethen-1-yl, (*E*)-2-(4-fluorophenyl)ethen-1-yl and (*E*)-3-phenylpropen-1-yl. Preferred examples are (*E*)-2-phenylethen-1-yl and (*E*)-2-(4-fluorophenyl)ethen-1-yl.

Preferred examples of groups wherein 'X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group' are benzylidene and benzylidene substituted in the phenyl ring with C_{1-7}-alkyl, C_{1-7}-alkyl-O- or halogen such as 4-methylbenzylidene, 3-methylbenzylidene, 2-methylbenzylidene, 4-methoxybenzylidene, 3-methoxybenzylidene, 2-methoxybenzylidene, 4-chlorobenzylidene, 3-chlorobenzylidene, 2-chlorobenzylidene, 4-fluorobenzylidene, 3-fluorobenzylidene, 2-fluorobenzylidene.

Preferred examples of R^4 and R^5 representing a 'saturated 4-, 5- or 6-membered ring including the nitrogen atom to which R^4 and R^5 are attached as ring atom' are azetidine, pyrrolidine, piperidine and morpholine.

Preferred examples of R^6 and R^7 representing 'a saturated carbocyclic ring including the carbon atom to which R^6 and R^7 are attached as ring atom' are 1,1-cyclopropane-diyl, 1,1-cyclobutane-diyl, 1,1-cyclopentane-diyl and 1,1-cyclohexane-diyl.

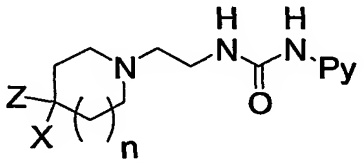
The present invention encompasses pharmaceutically acceptable salts of compounds of the General Formula 1. This encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, malic acid, methylsulfonic acid, p-tolylsulfonic acid and the like or in case the compound of formula 1 is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium, potassium, or calcium salts, etc. The compounds of General Formula 1 can also be present in form of zwitterions.

The present invention encompasses different solvation complexes of compounds of General Formula 1. The solvation can be effected in the course of the manufacturing process or can take place separately, e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of General Formula 1.

The present invention further encompasses different morphological forms, e.g. crystalline forms, of compounds of General Formula 1 and their salts and solvation complexes. Particular heteromorphs may exhibit different dissolution properties, stability profiles, and the like, and are all included in the scope of the present invention.

The compounds of the General Formula 1 might have one or more asymmetric carbon atoms and may be prepared in form of configurational isomers, optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates. The present invention encompasses all these forms. They are prepared by stereoselective synthesis, or by separation of mixtures in a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization, etc.

Preferred compounds of the invention are compounds of General Formula 2.



General Formula 2

wherein:

Py represents pyridin-4-yl which is disubstituted in positions 2 and 6, whereby the substituent in position 2 is C_{1-7}-alkyl or aryl-C_{1-7}-alkyl and the substituent in position 6 is methyl or ethyl;

X represents aryl; aryl-C_{1-7}-alkyl-; aryl-O-; aryl-C_{1-7}-alkyl-O-; R^1-SO_2NR^2-; R^1-$CONR^2$-; aryl-R^8-$CONR^2$-; R^1-NR^3CONR^2-; or R^1-NR^2CO-;

Z represents hydrogen; in case X represents aryl or aryl-C_{1-7}-alkyl and n represents the number 1 Z represents hydrogen, hydroxyl or R^4-NR^5CO-;

n represents the numbers 0 or 1;

R^1 represents aryl or aryl-C_{1-7}-alkyl;

R^2 represents hydrogen; C_{1-7}-alkyl; 2-hydroxyethyl; aryl-C_{1-7}-alkyl; or a saturated carbocyclic ring;

R^3 represents hydrogen or C_{1-7}-alkyl;

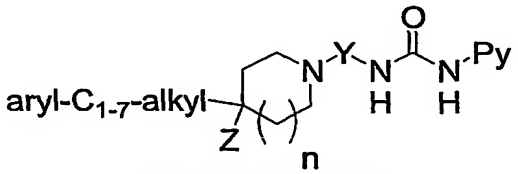
R^4 represents hydrogen; C_{1-7}-alkyl; aryl; aryl-C_{1-7}-alkyl; or forms together with R^5 a saturated 4-, 5- or 6-membered ring including the nitrogen atom to which R^4 and R^5 are attached as ring atom;

R^5 represents hydrogen; C_{1-7}-alkyl; 2-hydroxyethyl; or forms together with R^4 a saturated 4-, 5- or 6-membered ring including the nitrogen atom to which R^4 and R^5 are attached as ring atom.

R^8 represents a saturated carbocyclic ring.

In a preferred embodiement also the following forms are encompassed: optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

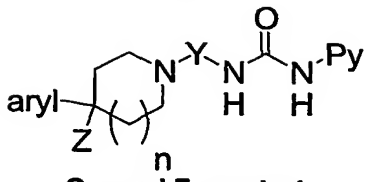
Preferred compounds of General Formula 1 are the compounds of General Formula 3:



General Formula 3

wherein n, Y, Z and Py have the meaning given in General Formula 1.

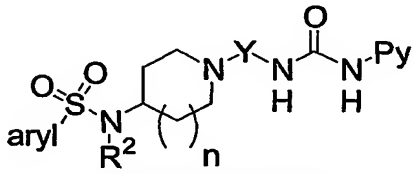
Preferred compounds of General Formula 1 are the compounds of General Formula 4:



General Formula 4

wherein n, Y, Z and Py have the meaning given in General Formula 1.

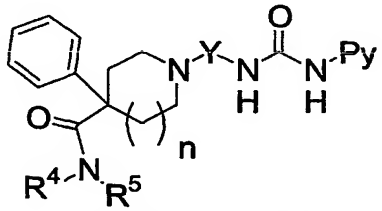
Preferred compounds of General Formula 1 are the compounds of General Formula 5:



General Formula 5

wherein R^2, Y, n and Py have the meaning given in General Formula 1.

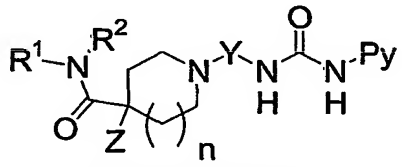
Preferred compounds of General Formula 1 are the compounds of General Formula 6:



General Formula 6

wherein R^4, R^5, Y, n and Py have the meaning given in General Formula 1.

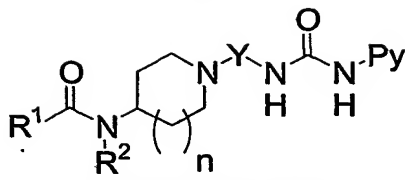
Preferred compounds of General Formula 1 are the compounds of General Formula 7:



General Formula 7

wherein R^1, R^2, Z, Y, n and Z have the meaning given in General Formula 1.

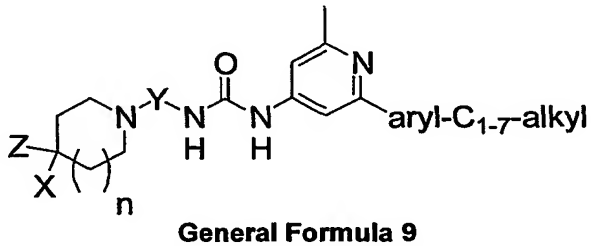
Preferred compounds of General Formula 1 are the compounds of General Formula 8:



General Formula 8

wherein R^1, R^2, n, Y and Py have the meaning given in General Formula 1.

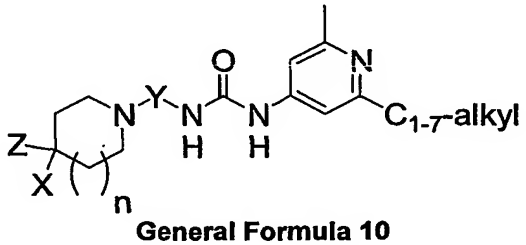
Preferred compounds of General Formula 1 are the compounds of General Formula 9:



General Formula 9

wherein X, Y, Z, n and Py have the meaning given in General Formula 1.

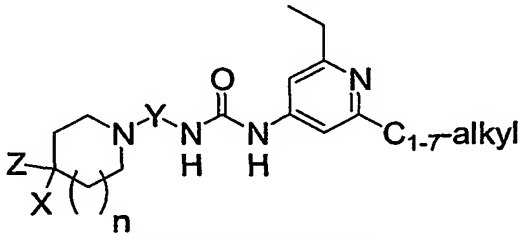
Preferred compounds of General Formula 1 are the compounds of General Formula 10:



General Formula 10

wherein X, Y, Z, n and Py have the meaning given in General Formula 1.

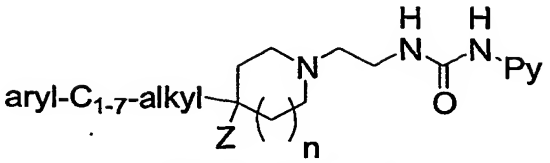
Preferred compounds of General Formula 1 are the compounds of General Formula 11:



General Formula 11

wherein X, Y, Z, n and Py have the meaning given in General Formula 1.

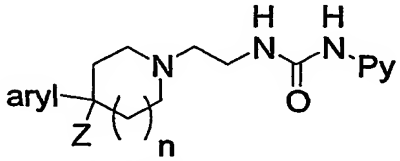
Preferred compounds of General Formula 2 are the compounds of General Formula 12:



General Formula 12

wherein n, Z and Py have the meaning given in General Formula 2.

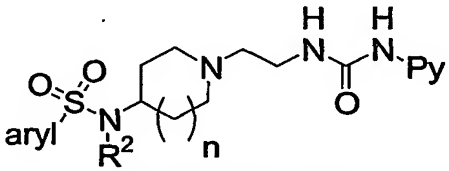
Preferred compounds of General Formula 2 are the compounds of General Formula 13:



General Formula 13

wherein n, Z and Py have the meaning given in General Formula 2.

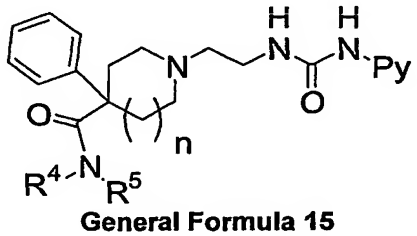
Preferred compounds of General Formula 2 are the compounds of General Formula 14:



General Formula 14

wherein R^2, n and Py have the meaning given in General Formula 2.

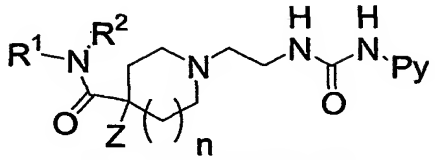
Preferred compounds of General Formula 2 are the compounds of General Formula 15:



General Formula 15

wherein R^4, R^5, n and Py have the meaning given in General Formula 2.

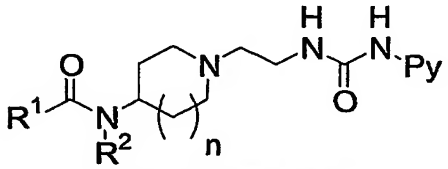
Preferred compounds of General Formula 2 are the compounds of General Formula 16:



General Formula 16

wherein R^1, R^2, Z, n and Z have the meaning given in General Formula 2.

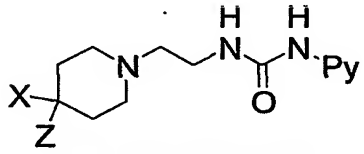
Preferred compounds of General Formula 2 are the compounds of General Formula 17:



General Formula 17

wherein R^1, R^2, n and Py have the meaning given in General Formula 2.

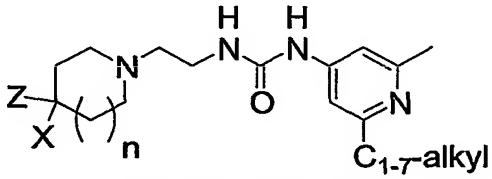
Preferred compounds of General Formula 2 are the compounds of General Formula 18:



General Formula 18

wherein X, Z and Py have the meaning given in General Formula 2.

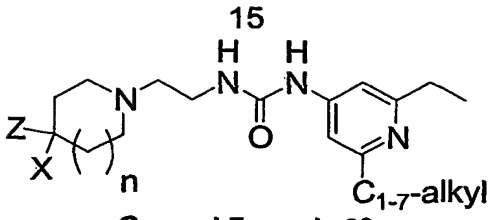
Preferred compounds of General Formula 2 are the compounds of General Formula 19:



General Formula 19

wherein X, Z and n have the meaning given in General Formula 2.

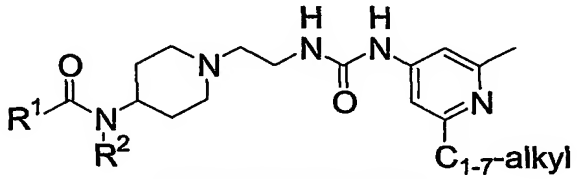
Preferred compounds of General Formula 2 are the compounds of General Formula 20:



General Formula 20

wherein X, Z and n have the meaning given in General Formula 2.

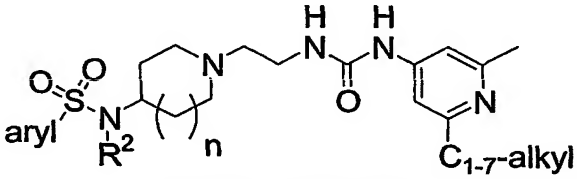
Preferred compounds of General Formula 2 are the compounds of General Formula 21:



General Formula 21

wherein R^1 and R^2 have the meaning given in General Formula 2.

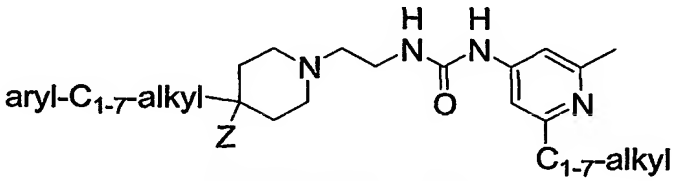
Preferred compounds of General Formula 2 are the compounds of General Formula 22:



General Formula 22

wherein R^2 and n have the meaning given in General Formula 2.

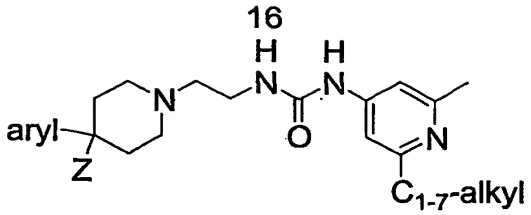
Preferred compounds of General Formula 2 are the compounds of General Formula 23:



General Formula 23

wherein Z has the meaning given in General Formula 2.

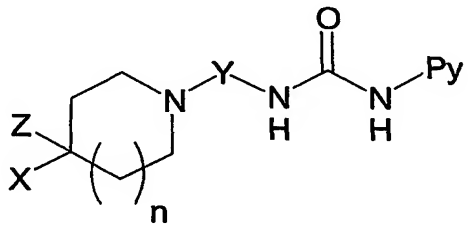
Preferred compounds of General Formula 2 are the compounds of General Formula 24:



General Formula 24

wherein Z has the meaning given in General Formula 2.

The present invention also relates to compounds of the General Formula 25:



General Formula 25

wherein:

Py represents pyridin-4-yl which is disubstituted in positions 2 and 6, whereby the substituent in position 2 is C_{1-7}-alkyl, aryl-C_{1-7}-alkyl, or (*E*)-2-aryl-ethen-1-yl, and the substituent in position 6 is hydrogen or C_{1-7}-alkyl;

X represents aryl; aryl-O-; aryl-C_{1-7}-alkyl-; R^1-SO_2NR^2-; R^1-$CONR^2$-; R^1-NR^3CONR^2-; R^1-NR^2CO-; or X and Z represent together with the carbon atom to which they are attached an exocyclic double bond which bears an aryl substituent at the thus formed methylene group;

Y represents $-C(R^4)(R^5)(CH_2)_m-$ or $-(CH_2)_mC(R^4)(R^5)-$;

Z represents hydrogen; in case X represents aryl or aryl-C_{1-7}-alkyl Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-; or in case X represents aryl or aryl-C_{1-7}-alkyl and n represents the number 0, Z represents hydrogen, hydroxyl, carboxyl, R^1-NR^2CO-, aryl, aryl-C_{1-7}-alkyl;

n represents the numbers 0 or 1;

m represents the numbers 1 or 2;

R^1 represents aryl; C_{1-7}-alkyl; aryl-C_{1-7}-alkyl; or a saturated carbocyclic ring;

R^2 and R^3 represent independently hydrogen; C_{1-7}-alkyl; aryl-C_{1-7}-alkyl; or a saturated carbocyclic ring;

R^4 represents hydrogen; C_{1-7}-alkyl; aryl; aryl-C_{1-7}-alkyl; or forms together with R^5 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

R^5 represents hydrogen; methyl; or forms together with R^4 a saturated carbocyclic ring including the carbon atom to which R^4 and R^5 are attached as ring atom;

and optically pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates, and mixtures of diastereomeric racemates; as well as their pharmaceutically acceptable salts, solvent complexes, and morphological forms.

In the definitions of the General Formula 25 the expression 'aryl' means a substituted or unsubstituted aromatic carbocyclic or heterocyclic ring system, consisting of a five- or six- membered aromatic ring, or of a fused five-six or six-six aromatic ring system. Preferred aryl groups are for example 2-furyl; 2-thienyl; phenyl; 2-methylphenyl; 2-biphenyl; 2-methoxyphenyl; 2-phenoxyphenyl; 2-chlorophenyl; 2-bromophenyl; 2-*i*-propylphenyl; 2-fluorophenyl; 2-methylsulfonylphenyl; 2-cyanophenyl; 2-trifluoromethylphenyl; 3-methylphenyl; 3-biphenyl; 3-phenoxyphenyl; 3-methoxyphenyl; 3-chlorophenyl; 3-bromophenyl; 3-fluorophenyl; 3-cyanophenyl; 3-trifluoromethylphenyl; 3-carboxyphenyl; 4-methylphenyl; 4-ethylphenyl; 4-*i*-propylphenyl; 4-phenyloxyphenyl; 4-trifluoromethylphenyl; 4-trifluoromethoxyphenyl; 4-phenoxyphenyl; 4-cyanophenyl; 4-hydroxyphenyl; 4-acetylaminophenyl; 4-methanesulfonylphenyl; 4-*n*-propylphenyl; 4-*iso*-propylphenyl; 4-*tert*-butylphenyl; 4-*n*-pentylphenyl; 4-biphenyl; 4-chlorophenyl; 4-bromophenyl; 4-bromo-2-ethylphenyl; 4-fluorophenyl; 2,4-difluorophenyl; 4-*n*-butoxyphenyl; 2,6-dimethoxyphenyl; 3,5-bis-trifluoromethylphenyl; 2-pyridyl; 3-pyridyl; 4-pyridyl; 1-naphthyl; 2-naphthyl; 4-(pyrrol-1-yl)phenyl; 4-benzoylphenyl; 5-dimethylaminonaphth-1-yl; 5-chloro-3-methylthiophen-2-yl; 5-chloro-3-methyl-benzo[b]thiophen-2-yl; 3-(phenylsulfonyl)-thiophen-2-yl; 2-(2,2,2-trifluoroacetyl)-1-2,3,4-tetrahydroisoquinolin-7-yl; 4-(3-chloro-2-cyanophenyloxy)phenyl; 2-(5-benzamidomethyl)thiophenyl; 4,5-

dichlorothien-2-yl; 5-quinolyl-; 6-quinolyl; 7-quinolyl; 8-quinolyl; (2-acetylamino-4-methyl)thiazol-5-yl; or 1-methylimidazol-4-yl.

In the definitions of the General Formula 25 the expression 'C_{1-7}-alkyl' means straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms. Preferred examples of C_{1-7}-alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, and n-heptyl.

In the definitions of the General Formula 25 the expression 'saturated carboxyclic ring' means a saturated cyclic alkyl group with three to six carbon atoms. Preferred examples of saturated carbocyclic rings are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In the definitions of the General Formula 25 the expression 'aryl-C_{1-7}-alkyl' means a C_{1-7}-alkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred examples of aryl-C_{1-7}-alkyl groups are 3-phenylpropyl, phenethyl, benzyl and benzyl substituted in the phenyl ring with hydroxy, C_{1-7}-alkyl, C_{1-7}-alkyloxy, or halogen.

Examples of particularly preferred compounds of General Formula 1 are selected from the group consisting of:

Example number	
1	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea
2	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
3	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide
4	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide
5	1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(3,3-diphenyl-pyrrolidin-1-yl)-ethyl]-urea
6	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-

	urea
15	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide
16	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide
17	1-(2-{3-[2-Methyl-6-((*E*)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
22	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
23	1-{2-[3-(2-Methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
24	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-6-propyl-pyridin-4-yl)-urea
25	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
26	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea
27	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide
28	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
35	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea
36	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-pyridin-4-yl}-urea
37	1-{2-[3-(2-Methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
7	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide
8	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-benzenesulfonamide
11	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide

12	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide
30	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-benzenesulfonamide
31	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-diethyl-pyridin-4-yl)-urea
33	*N*-(1-{2-[3-(2,6-Diethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide
34	*N*-(1-{2-[3-(2,6-Diethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide
41	*N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide
42	4-Bromo-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
43	*N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide
49	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-methyl-benzenesulfonamide
60	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-ethyl-*N*-methyl-benzenesulfonamide
61	*N*-{4-[(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-sulfamoyl]-phenyl}-acetamide
62	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-isopropoxy-*N*-methyl-benzenesulfonamide
63	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4,*N*-dimethyl-benzenesulfonamide
67	4-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide
70	3,4-Dichloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide
71	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-4-trifluoromethyl-benzenesulfonamide

74	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
75	2,5-Dichloro-thiophene-3-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
76	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide
77	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-fluoro-benzenesulfonamide
78	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-fluoro-benzenesulfonamide
79	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,4-difluoro-benzenesulfonamide
80	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-difluoro-benzenesulfonamide
81	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,6-difluoro-benzenesulfonamide
82	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4,*N*-diethyl-benzenesulfonamide
83	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-isopropoxy-benzenesulfonamide
84	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methyl-benzenesulfonamide
85	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-methyl-benzenesulfonamide
86	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methyl-benzenesulfonamide
87	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-2,3,6-trimethyl-benzenesulfonamide
88	4-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide
89	3-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-

	N-ethyl-benzenesulfonamide
90	2-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide
91	3,4-Dichloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide
92	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-trifluoromethyl-benzenesulfonamide
93	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-trifluoromethyl-benzenesulfonamide
94	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-trifluoromethyl-benzenesulfonamide
95	Thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
96	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
97	2,5-Dichloro-thiophene-3-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
98	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,5-dimethoxy-benzenesulfonamide
99	5-Bromo-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide
100	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-4-methyl-benzenesulfonamide
101	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-dimethoxy-benzenesulfonamide
102	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-methoxy-benzenesulfonamide
103	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
104	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-fluoro-benzenesulfonamide

106	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,4-difluoro-benzenesulfonamide
108	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,6-difluoro-benzenesulfonamide
109	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-ethyl-benzenesulfonamide
111	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-isopropoxy-benzenesulfonamide
112	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methyl-benzenesulfonamide
113	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methyl-benzenesulfonamide
115	4-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
116	3-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
117	2-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
118	3,4-Dichloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide
119	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide
120	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-trifluoromethyl-benzenesulfonamide
123	5-Chloro-thiophene-2-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
124	2,5-Dichloro-thiophene-3-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
125	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide
126	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-

	piperidin-4-yl)-3-methoxy-benzenesulfonamide
127	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,5-dimethoxy-benzenesulfonamide
128	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4-methyl-benzenesulfonamide
129	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4-methyl-benzenesulfonamide
130	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-dimethoxy-benzenesulfonamide
131	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methoxy-benzenesulfonamide
135	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
144	2-(4-Chloro-phenyl)-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-isobutyramide
146	2-(3,4-Dichloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide
148	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-isobutyramide
150	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
163	1-Phenyl-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
164	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
167	2-(4-Chloro-phenyl)-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide
168	2-(4-Chloro-phenyl)-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-isobutyramide
170	2-(4-Chloro-phenyl)-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide

171	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
172	1-Phenyl-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
173	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide

Examples of particularly preferred compounds of General Formula 1 are selected from the group consisting of:

Example number	
9	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-(4-methoxy-phenyl)-acetamide
13	4-Ethyl-1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide
29	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea
32	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-diethyl-pyridin-4-yl)-urea
48	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide
50	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methoxy-*N*-methyl-benzenesulfonamide
52	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-dimethoxy-*N*-methyl-benzenesulfonamide
53	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4,*N*-dimethyl-benzenesulfonamide
54	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-methyl-benzenesulfonamide
55	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-fluoro-*N*-methyl-benzenesulfonamide

56	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-fluoro-*N*-methyl-benzenesulfonamide
57	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,4-difluoro-*N*-methyl-benzenesulfonamide
58	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-difluoro-*N*-methyl-benzenesulfonamide
59	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,6-difluoro-*N*-methyl-benzenesulfonamide
64	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,*N*-dimethyl-benzenesulfonamide
65	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,*N*-dimethyl-benzenesulfonamide
66	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-2,3,6,*N*-tetramethyl-benzenesulfonamide
68	3-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide
69	2-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide
72	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-3-trifluoromethyl-benzenesulfonamide
73	Thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
105	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-fluoro-benzenesulfonamide
107	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-difluoro-benzenesulfonamide
114	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methyl-benzenesulfonamide
121	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethyl-benzenesulfonamide
122	Thiophene-2-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-

	ureido]-ethyl}-piperidin-4-yl)-amide
132	2-(3,4-Dichloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide
134	1-Phenyl-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
136	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide
138	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide
139	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-(4-fluoro-phenyl)-*N*-methyl-acetamide
140	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-2-phenyl-acetamide
142	2-(3-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide
145	2-(2-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide
147	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(2-methoxy-phenyl)-acetamide
149	1-Phenyl-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
151	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide
152	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-phenyl-acetamide
153	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(4-methoxy-phenyl)-acetamide
154	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzamide
155	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-dimethoxy-benzamide

156	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzamide
157	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(3-methoxy-phenyl)-acetamide
158	2-(3,4-Dimethoxy-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide
160	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-thiophen-2-yl-acetamide
161	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(4-fluoro-phenyl)-acetamide
162	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzamide
165	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide
166	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide
169	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide

Because of their ability to inhibit the actions of urotensin II, the described compounds can be used for treatment of diseases which are associated with an increase in vasoconstriction, proliferation or other disease states associated with the actions of urotensin II. Examples of such diseases are hypertension, atherosclerosis, angina or myocardial ischemia, congestive heart failure, cardiac insufficiency, cardiac arrhythmias, renal ischemia, chronic kidney disease, renal failure, stroke, cerebral vasospasm, cerebral ischemia, dementia, migraine, subarachnoidal hemorrhage, diabetes, diabetic arteriopathy, diabetic nephropathy, connective tissue diseases, cirrhosis, chronic obstructive pulmonary disease, high-altitude pulmonary edema, Raynaud's syndrome, portal hypertension, thyroid dysfunction, pulmonary edema, pulmonary hypertension, or pulmonary fibrosis. They can also be used for prevention of restenosis after balloon or stent angioplasty, for the treatment of cancer, prostatic hypertrophy, erectile

dysfunction, hearing loss, amaurosis, chronic bronchitis, asthma, gram negative septicemia, shock, sickle cell anemia, sickle cell acute chest syndrome, glomerulonephritis, renal colic, glaucoma, therapy and prophylaxis of diabetic complications, complications of vascular or cardiac surgery or after organ transplantation, complications of cyclosporin treatment, pain, addiction, schizophrenia, Alzheimer's disease, anxiety, obsessive-compulsive behavior, epileptic seizures, stress, depression, dementias, neuromuscular disorders, neurodegenerative diseases, as well as other diseases related to a dysregulation of urotensin II or urotensin II receptors.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays and aerosols, or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula 1 as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients, which are usual in the pharmaceutical industry, like lactose, maize or derivatives thereof, talcum, stearic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants etc.

The compounds of General Formula 1 may also be used in combination with one or more other therapeutically useful substances e.g. α- and β-blockers like

phentolamine, phenoxybenzamine, atenolol, propranolol, timolol, metoprolol, carteolol, carvedilol, etc.; with vasodilators like hydralazine, minoxidil, diazoxide, flosequinan, etc.; with calcium-antagonists like diltiazem, nicardipine, nimodipine, verapamil, nifedipine, etc.; with angiotensin converting enzyme-inhibitors like cilazapril, captopril, enalapril, lisinopril etc.; with potassium channel activators like pinacidil, chromakalim, etc.; with angiotensin receptor antagonists like losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan, and tasosartan, etc.; with diuretics like hydrochlorothiazide, chlorothiazide, acetolamide, bumetanide, furosemide, metolazone, chlortalidone, etc.; with sympatholytics like methyldopa, clonidine, guanabenz, reserpine, etc.; with endothelin receptor antagonists like bosentan, tezosentan, darusentan, atrasentan, enrasentan, or sitaxsentan, etc.; with anti-hyperlipidemic agents like lovastatin, pravistatin, fluvastatin, atorvastatin, cerivastatin, simvastatin, etc.; and other therapeutics which serve to treat high blood pressure, vascular disease or other disorders listed above.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given daily in oral form should be between about 3 mg and about 3 g, preferably between about 5 mg and about 1 g, especially preferred between 10 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses of equal weight per day. As usual children should receive lower doses which are adapted to body weight and age.

GENERAL PREPARATION OF COMPOUNDS OF THE INVENTION

Compounds of the General Formula 1 can be prepared using methods generally known in the art, according to the general sequence of reactions outlined below. For simplicity and clarity reasons sometimes only a few of the possible synthetic routes that lead to compounds of General Formula 1 are described.

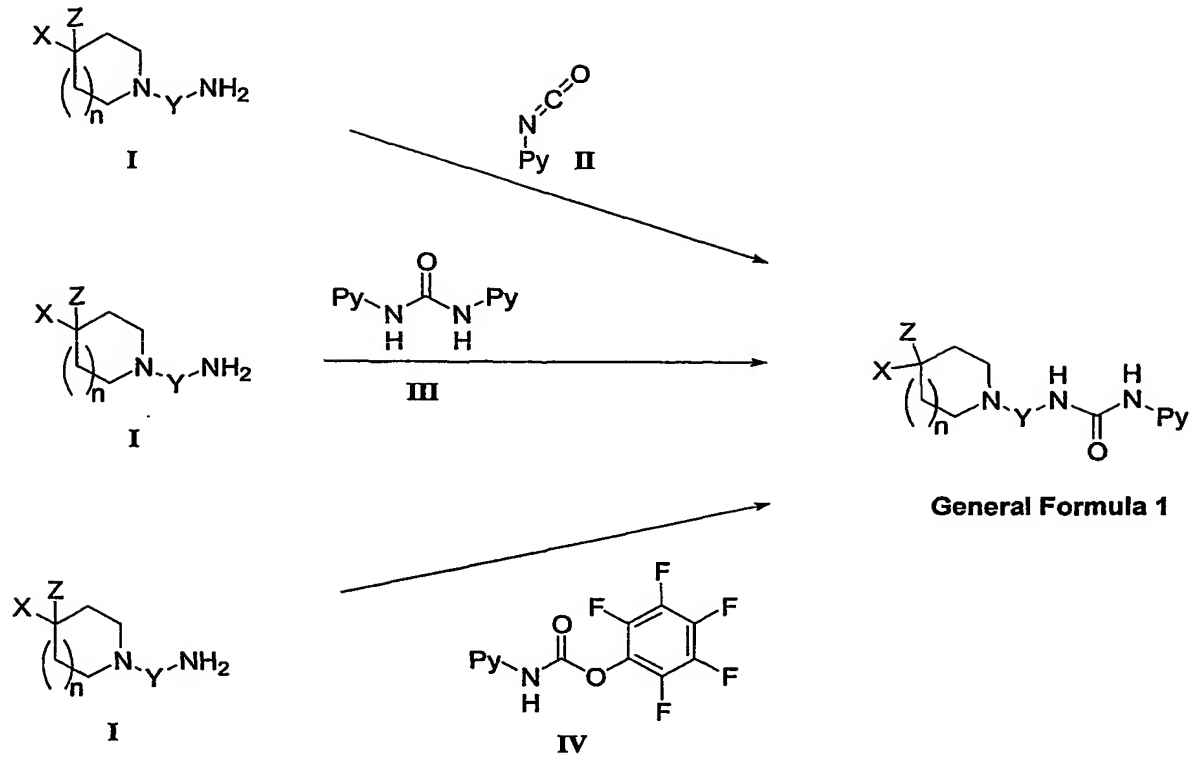
For the synthesis of compounds of General Formula 1 general synthetic routes illustrated in schemes A through G can be employed. The generic groups Py, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X, Y, Z, n, and m employed in schemes A through G have the definitions given in General Formula 1 above. Other abbreviations used are defined in the experimental section. Some instances of the generic groups X and Z might be incompatible with the assembly illustrated in schemes A through G

and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that such protecting groups as are necessary are in place.

Preparation of compounds of General Formula 1. These compounds are prepared according to scheme A.

Achiral, racemic or enantiomerically pure amines of general structure I in scheme A are reacted with isocyanates of general structure II to provide compounds of General Formula 1. Alternatively, amines of general structure I are reacted with ureas of general structure III to provide compounds of General Formula 1. Alternatively, amines of general structure I are reacted with pentafluorophenyl-carbamates of general structure IV to provide compounds of General Formula 1. The preparation of isocyanates of general structure II, of ureas of general structure III and of pentafluorophenyl-carbamates of general structure IV is described in scheme E below. The preparation of amines of general structure I is described in scheme G below.

Scheme A

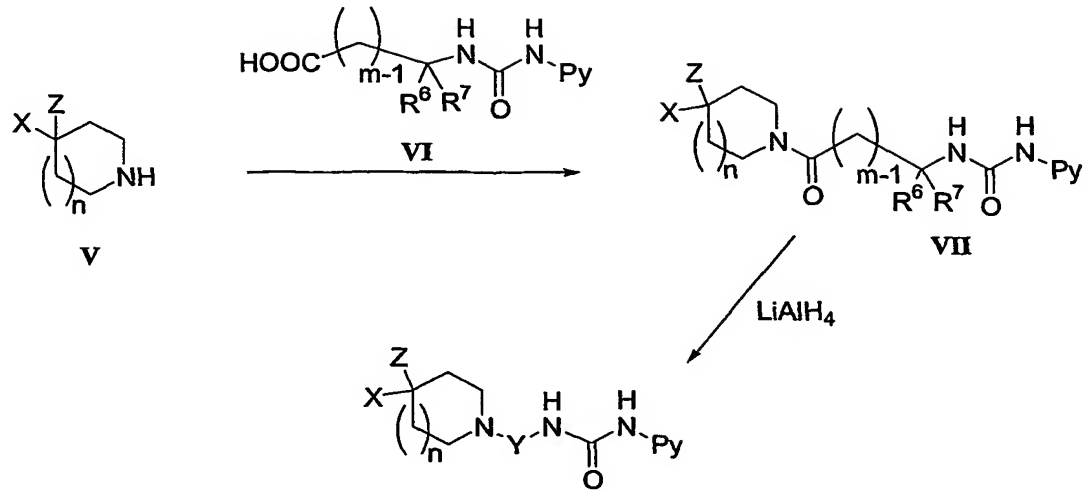


Preparation of compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^6)(R^7)$-.

Compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^6)(R^7)$- are prepared according to scheme B.

Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure V in scheme B are either commercially available or prepared by methods well known in the art. Ureido acetic- and propionic acid derivatives of general structure VI in scheme B are prepared according to scheme F below. *N*-Acylation of piperidines and pyrrolidines of general structure V with ureido acetic- and propionic acid derivatives of general structure VI is accomplished in a polar solvent such as DMF in the presence of a small stoichiometric excess of a coupling reagent such as a EDC to provide amides of general structure VII. Selective reduction of the amide carbonyl group with a reagent such as $LiAlH_4$ in a aprotic solvent such as THF provides the target compounds of General Formula 1 wherein Y is -$(CH_2)_mC(R^6)(R^7)$-.

Scheme B

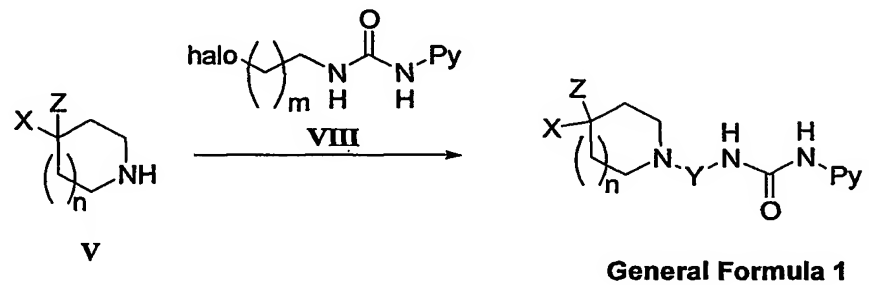


General Formula 1

wherein Y = $-(CH_2)_m-C(R^6)(R^7)-$

Compounds of General Formula 1 wherein R^6 and R^7 are H. These compounds are alternatively prepared according to the method illustrated in scheme C.

Scheme C



General Formula 1

wherein R^6 and R^7 = H

Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure V in scheme C are either commercially available or prepared by methods well known in the art. Haloalkyl ureas of general structure VIII in scheme C are prepared according to scheme E below. *N*-Alkylation of piperidines and pyrrolidines of general structure V with haloalkyl ureas of general structure VIII is accomplished in a polar solvent such as tetrahydrofuran in the presence of a sub-stoichiometric amount of an iodide salt such as NaI and a small

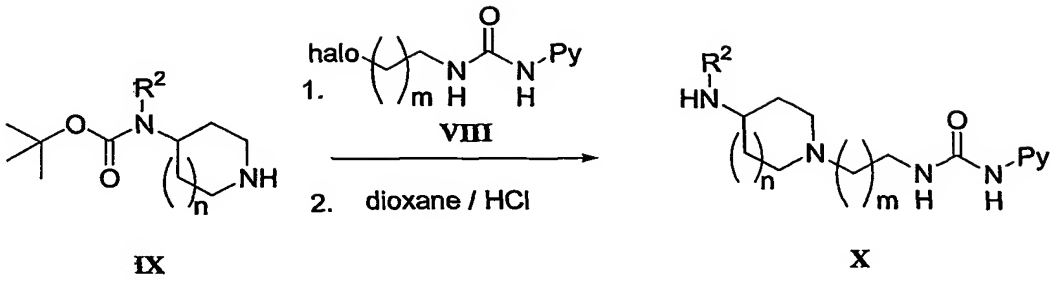
stoichiometric excess of acid scavenger such as $NaHCO_3$ to provide the target compounds of General Formula 1.

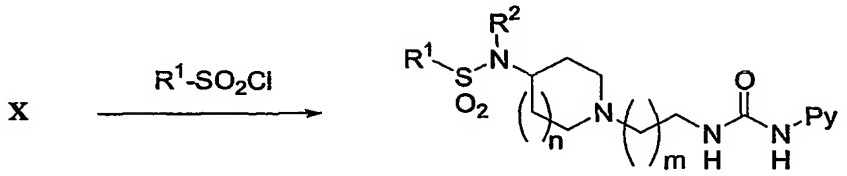
Compounds of General Formula 1 wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, aryl-R^8-$CONR^2$- or R^1-NR^2CONR^3- and Z, R^6 and R^7 represent H. These compounds are alternatively prepared according to the method illustrated in scheme D.

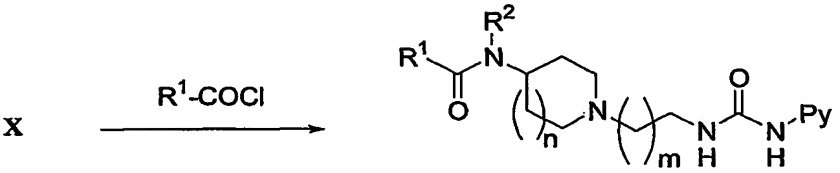
Achiral, racemic or optically active carbamates of general structure IX in scheme D are either commercially available or readily prepared by methods well known in the art. Haloalkyl ureas of general structure VIII are prepared according to Scheme E below. Carbamates of general structure IX are reacted with haloalkyl ureas of general structure VIII in a polar solvent such as tetrahydrofuran in the presence of a substoichiometric amount of an iodide salt such as NaI and a small stoichiometric excess of an acid scavenger such as $NaHCO_3$, followed by removal of the carbamate group under acidic conditions, such as reaction with HCl in dioxane or TFA in CH_2Cl_2.

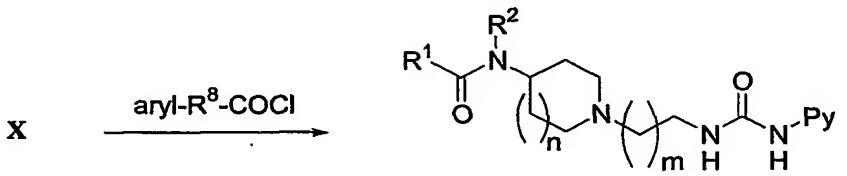
The resulting compounds of general structure X in scheme D are converted to compounds of General Formula 1 wherein X represents R^1-SO_2NR^2-, R^1-$CONR^2$-, aryl-R^8-$CONR^2$- or R^1-NR^2CONR^3- and Z, R^6 and R^7 represent H, by reaction with commercially available or well known sulfonylchlorides, isocyanates, or acid chlorides. Compounds of General Formula 1 wherein X represents R^1-NR^3CONR^2-, R^3 represents C_{1-7}-alkyl or aryl-C_{1-7}-alkyl, and Z, R^6 and R^7 represent H, are prepared by reaction of compounds of general structure X with secondary amines that are commercially available or prepared by methods well known in the art in the presence of a stoichiometric amount of a coupling reagent such as carbonyldiimidazole (CDI).

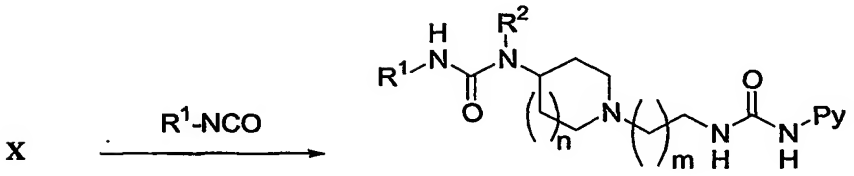
Scheme D

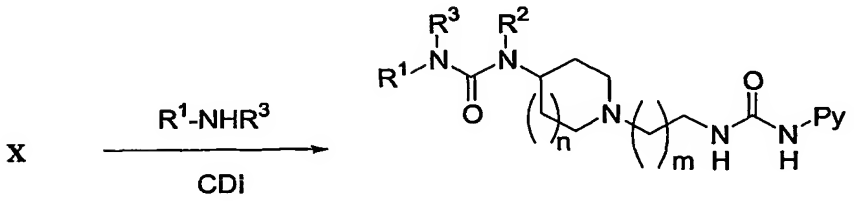

halo
1.
VIII
2. dioxane / HCl
IX
X


X
R1-SO2Cl


X
R1-COCl


X
aryl-R8-COCl

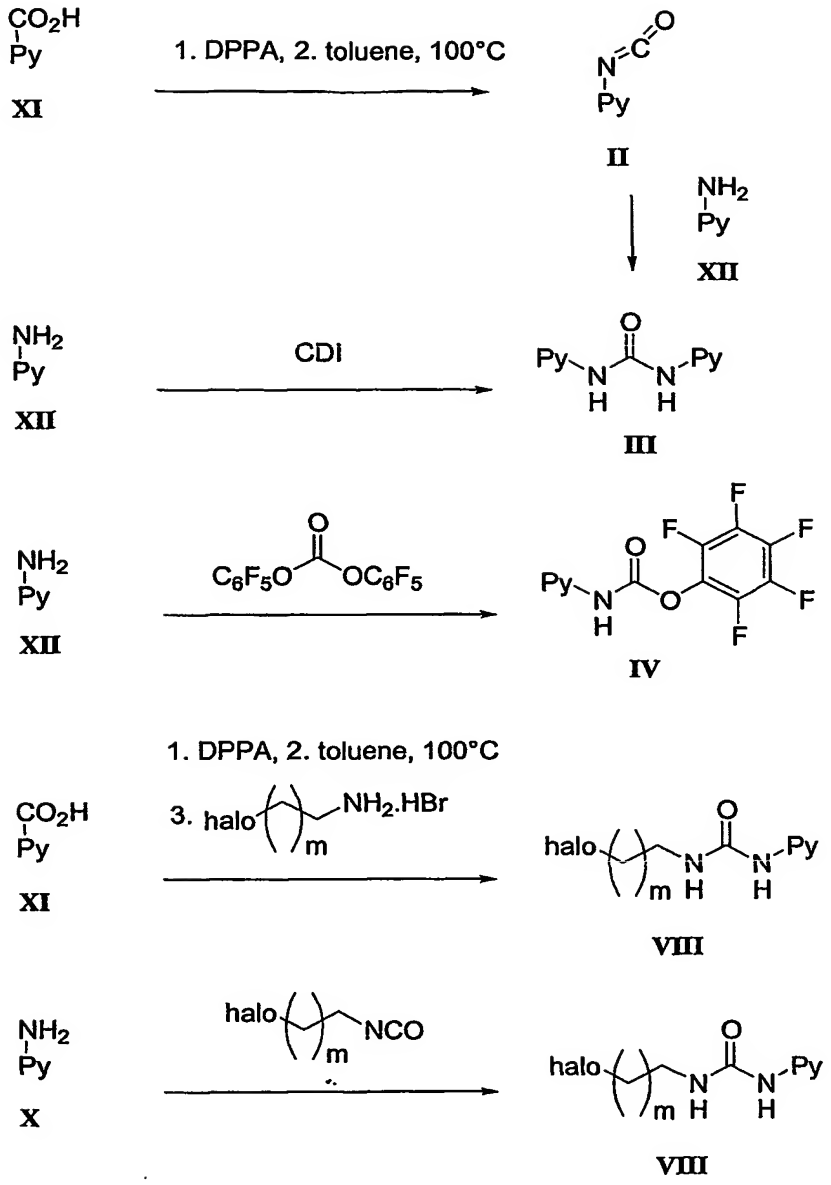

X
R1-NCO


X
R1-NHR3
CDI

Synthetic intermediates used in Schemes A, B, C, and D. Synthetic intermediates containing the group Py, as defined in the General Formula 1 above, are obtained by the methods illustrated in Schemes E and F.

Carboxylic acids of general structure XI in scheme E are commercially available or are prepared by well known methods. Reaction with diphenylphosphorylazide provides the acyl azide, which undergoes Curtius rearrangement to provide the isocyanates of general structure II, which are used in situ. 4-Aminopyridines of general structure XII are commercially available or prepared by methods well known in the art (see for example "A Convenient Preparation of 4-Pyridinamine Derivatives, M. Malinowski, L.Kaczmarek, J. Prakt. Chem. (1988) 330, 154-158). Reaction of 4-aminopyridines of general structure XII with isocyanates of general structure II provides ureas of general structure III. Alternatively, ureas of general structure III are prepared by reaction of 4-aminopyridines of general structure XII and a coupling reagent such as CDI in a aprotic solvent such as THF at reflux. Alternatively, pentafluorophenyl-carbamates of general structure IV are prepared by reaction of 4-aminopyridines of general structure XII and di(pentafluorophenyl)carbonate in a aprotic solvent such as THF at room temperature. Isocyanates of general structure II, reacted with halopropylamine hydrochloride or haloethylamine hydrochloride in the presence of an acid scavenger such as DIPEA, provide ureas of general structure VIII. Alternatively, reaction of 4-aminopyridines of general structure XII with chloroethylisocyanate or chloropropylisocyanate in a polar aprotic solvent such as tetrahydrofuran provides the ureas of general structure VIII.

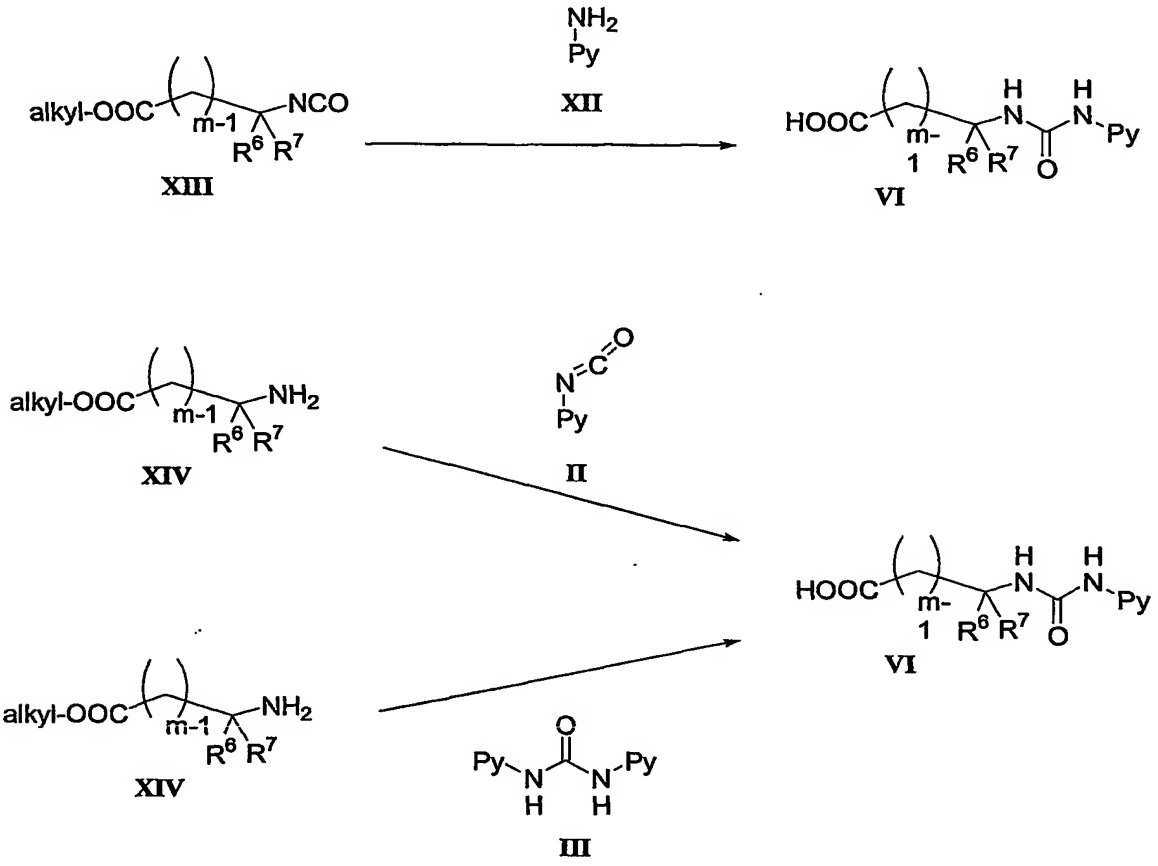
Scheme E



2- or 3-Isocyanato-carboxylic acid esters of general structure XIII in scheme F are commercially available or prepared by methods well known in the art. Amino acid esters of general structure XIV are commercially available or prepared by methods well known in the art. Reaction of amines of general structure XII with 2- or 3-isocyanato-carboxylic acid esters of general structure XIII in a polar aprotic solvent such as tetrahydrofuran, followed by hydrolysis of the ester in aqueous acid such as HCl, provides carboxylic acids of general structure VI. Alternatively, isocyanates of general structure II and ureas of general structure III react with

amino acid esters of general structure XIV to provide, after hydrolysis of the ester in aqueous acid such as HCl, carboxylic acids of general structure VI.

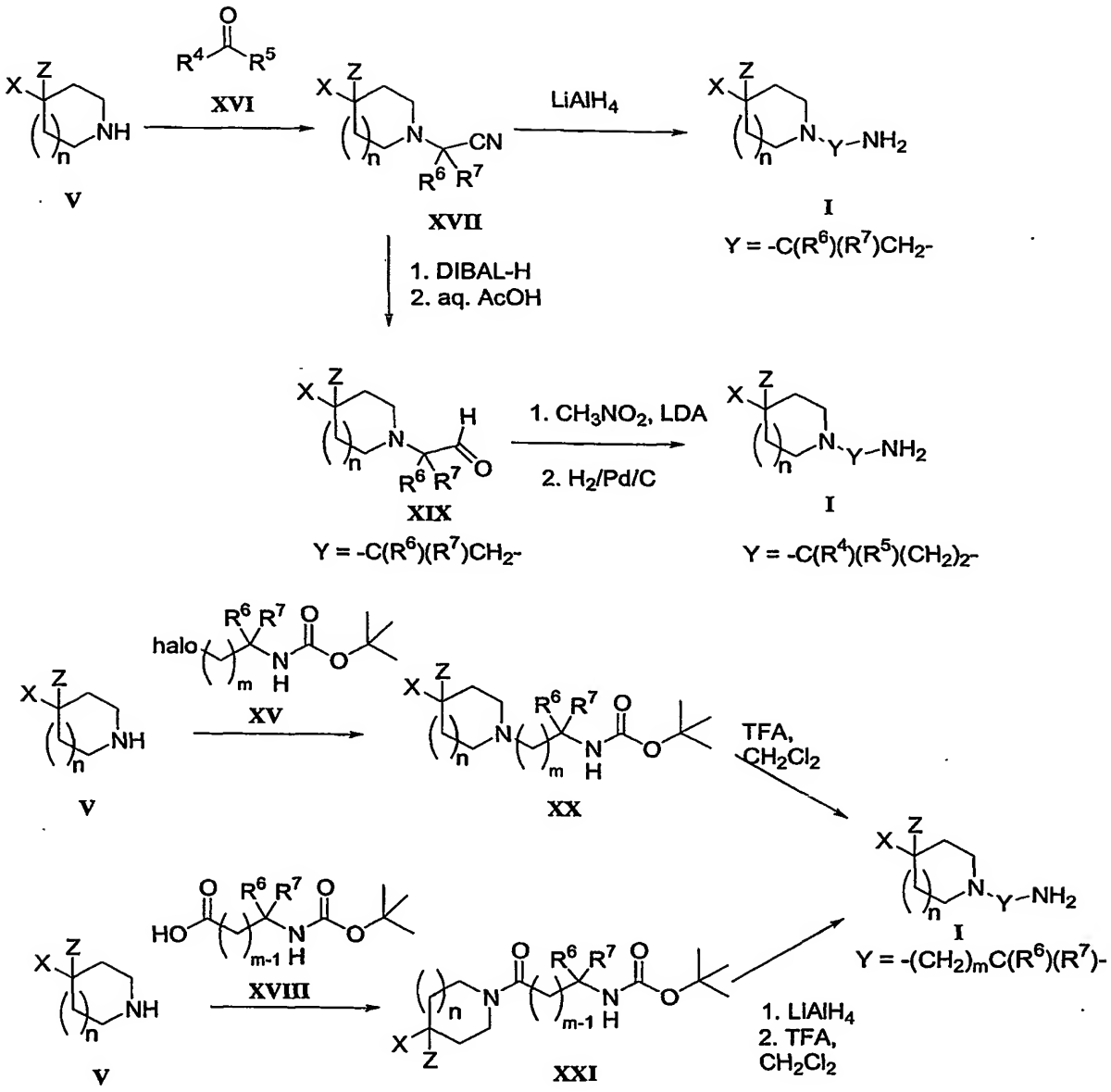
Scheme F



Synthetic intermediates of general structure I are obtained by the methods illustrated in Scheme G.

Achiral, racemic or optically active 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure V in scheme G are either commercially available or prepared by methods well known in the art. Ketones and aldehydes of general structure XVI are commercially available or are prepared by methods well-known in the art. Reaction of ketones and aldehydes of general structure XVI with 4-substituted-piperidines and 3-substituted-pyrrolidines of general structure V in presence of a cyanide ion donor such as acetone cyanohydrine provides piperidine and pyrrolidine derivatives of general structure XVII.

Scheme G



Alternatively, in case R^6 and R^7 represent H, compounds of general structure XVII are obtained by alkylation of compounds of general structure V with commercially available haloacetonitrile or 3-halopropionitrile in presence of a small stoichiometric excess of acid scavenger such as DIPEA. Complete reduction of the cyano group with a reducing reagent such as $LiAlH_4$ in a polar aprotic solvent such as THF provides the intermediate primary amines of general structure I, wherein Y is $-C(R^6)(R^7)-CH_2-$. Partial reduction of the cyano group of compounds of general structure XVII with a reducing reagent such as DIBAL-H, followed by aqueous hydrolysis provides aldehydes of general structure XIX. Condensation

with the nitromethane anion and subsequent reduction, for example by catalytic hydrogenation, provides the intermediate primary amines of general structure I, wherein Y is $-C(R^6)(R^7)(CH_2)_2-$. Haloalkyl carbamates of general structure XV in Scheme G are commercially available or are prepared by methods well-known in the art. *N*-Alkylation of piperidines and pyrrolidines of general structure V with haloalkyl carbamates of general structure XV is accomplished in a polar solvent such as THF in the presence of a small stoichiometric excess of acid scavenger such as DIPEA to provide compounds of general structure XX. Cleavage of the resulting carbamate with methods well known in the art, for example with TFA in a solvent such as CH_2Cl_2, provides the intermediate primary amine derivatives of general structure I wherein Y is $-(CH_2)_mC(R^6)(R^7)-$. Protected amino acids of general structure XVIII are commercially available or are prepared by methods well-known in the art. *N*-Acylation of piperidines and pyrrolidines of general structure V with compounds of general structure XVIII is accomplished under well-known conditions, for example in a polar solvent such as DMF in the presence of a small stoichiometric excess of a coupling agent such as a carbodiimide, to provide compounds of general structure XXI. Reduction with a reagent such as $LiAlH_4$ and deprotection provides intermediate primary amines of general structure I wherein Y is $-(CH_2)_mC(R^6)(R^7)-$.

The foregoing general description of the invention will now be further illustrated with a number of non-limiting examples.

EXAMPLES OF THE INVENTION

LIST OF ABBREVIATIONS:

AcOH	acetic acid
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BSA	bovine serum albumin
cat.	catalytic
CDI	carbonyldiimidazole
DIBAL-H	diisobutylaluminiumhydride

DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide
EDTA	ethylenediamine tetra-acetic acid
EtOAc	ethyl acetate
Et_2O	diethyl ether
FC	flash chromatography
$Fe(acac)_3$	iron(III)-acetylacetonate
Hex	hexane
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
h-UII	human Urotensin II
HV	high vacuum conditions
LC-MS	liquid chromatography-mass spectroscopy
$LiAlH_4$	lithium aluminum hydride
MeOH	methanol
min	minutes
MHz	megahertz
MPLC	medium pressure liquid chromatography
$NaBHAc_3$	sodium triacetoxyborohydride
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
ppm	part per million

PBS	phosphate-buffered saline
$Pd(dppf)Cl_2$	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
PG	protecting group
r.t.	room temperature
sat.	saturated
SiO_2	silica gel
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
t_R	retention time

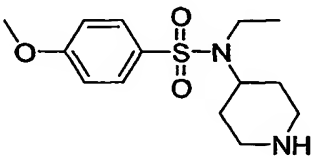
Reactions are routinely performed under an inert atmosphere such as N_2 gas in air dried glassware. Solvents are used as received from the vendor. Evaporations are performed in a rotary evaporator at reduced pressure and a water bath temperature of 50 °C. LC-MS characterizations are performed on a Finnigan HP1100 platform using ESI ionization mode, and positive ion detection with a Navigator AQA detector. Analytical liquid chromatographic separations are performed on a C18 column of 4.6 x 30 mm dimensions and a mobile phase consisting of a 6 minute gradient of 2 – 95% CH_3CN in water containing 0.5% formic acid at a flow rate of 0.45 mL/min. Retention time (t_R) is given in min. TLC is performed on pre-coated silica gel 60 F_{254} glass-backed plates (Merck). MPLC is performed on a Labomatic platform using either normal phase SiO_2-columns and a mobile phase consisting of heptane-EtOAc, or reversed phase C18 columns and a mobile phase consisting of water-MeOH. Preparative HPLC is performed on a Varian/Gilson platform using a C18 column of 21 x 60 mm dimensions and a mobile phase consisting of a gradient of 2 - 95% CH_3CN in water containing 0.5% formic acid.

Preparation of Intermediates. Example A.

The following materials are commercially available.

Example No	Example
A1.	4-Benzylpiperidine
A2.	4-Benzyl-piperidin-4-ol
A3.	4-Benzyloxy-piperidine

A4. *N*-Ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide.



A4.1. 4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester.

A mixture of commercially available 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (5.58 g, 28 mmol) and ethylamine (2 M in THF, 50 mL, 100 mmol) in THF (100 mL) is stirred at r.t. for 2 h. $NaBHAc_3$ (8.9 g, 42 mmol) is added and the mixture is stirred for 15 h. The mixture is quenched with 1 M aq. NaOH (100 mL) and stirred at r.t. for 6 h. The mixture is extracted with CH_2Cl_2 (150 mL, then 4 x 50 mL) and the combined organic extracts are washed with 1 M aq. NaOH (30 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated. The residue is dissolved in CH_2Cl_2 (100 mL) and TEA (3 g, 30 mmol) and, subsequently, a solution of 4-methoxy-benzenesulfonylchloride (6.38 g, 30.9 mmol) in CH_2Cl_2 (10 mL) are added at 0°C. The mixture is warmed to r.t. during 15 h and quenched with 1 M aq. NaOH (30 mL). The phases are separated and the organic phase is washed with 1 M aq. NaOH (30 mL), 1 M aq. $KHSO_4$ (2 x 30 mL) and sat. aq. NaCl (30 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

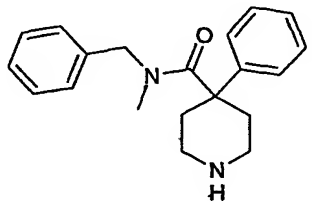
A4.2. *N*-Ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide.

A solution of 4-[ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester (11.1 g, 28 mmol) in CH_2Cl_2 (50 mL) is cooled at 0°C and TFA (40 mL) is added. The mixture is stirred at 0°C for 0.5 h and then evaporated. The residue is dissolved in CH_2Cl_2 (50 mL) and 1 M aq. NaOH (50 mL) is added. The mixture is stirred for 15 h at r.t., then the phases are separated and the aq. phase is extracted with CH_2Cl_2 (4 x 30 mL). The combined org. phases are washed with 1 M aq. NaOH (2 x 30 mL), dried (Na_2SO_4), filtered and evaporated to provide the title compound.

The following intermediates are prepared from 4-oxo-piperidine-1-carboxylic acid tert-butyl ester, ethylamine, cyclopropylamine or n-propylamine, and commercially available arylsulfonylchlorides or arylacetyl chlorides using the method described in Example A4.

Example No	Example
A4.	*N*-Ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide
A5.	*N*-Ethyl-4-fluoro-*N*-piperidin-4-yl-benzenesulfonamide
A6.	4-Bromo-*N*-ethyl-*N*-piperidin-4-yl-benzenesulfonamide
A7.	4-Methoxy-*N*-piperidin-4-yl-*N*-propyl-benzenesulfonamide
A8.	4-Fluoro-*N*-piperidin-4-yl-*N*-propyl-benzenesulfonamide
A9.	*N*-Cyclopropyl-4-fluoro-*N*-piperidin-4-yl-benzenesulfonamide
A10.	2-(4-Chloro-phenyl)-*N*-ethyl-*N*-piperidin-4-yl-acetamide
A11.	*N*-Cyclopropyl-2-(4-methoxy-phenyl)-*N*-piperidin-4-yl-acetamide

A12. 4-Phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.



A12.1. 4-Phenyl-piperidine-1,4-dicarboxylic acid monobenzyl ester.

A suspension of commercially available 4-phenyl-4-carboxypiperidine toluenesulfonate (7.55 g, 20 mmol), *N*-(benzyloxycarbonyloxy)succinimide (5.0 g, 20 mmol) and TEA (5 mL, 36 mmol) in $CHCl_3$ (100 mL) is stirred at r.t. for 48 h. The mixture is diluted with CH_2Cl_2 (100 mL) and extracted with 1 M aq. NaOH (3 x 50 mL). The aq. phase is extracted with Et_2O (2 x 50 mL), acidified (pH 2) with 6N aq. HCl and extracted with CH_2Cl_2 (4 x 50 mL). The combined CH_2Cl_2 extracts are dried (Na_2SO_4), filtered and evaporated to provide the title compound.

A12.2. 4-(Benzyl-methyl-carbamoyl)-4-phenyl-piperidine-1-carboxylic acid benzyl ester.

A mixture of 4-phenyl-piperidine-1,4-dicarboxylic acid monobenzyl ester (3.39 g, 10 mmol) and $SOCl_2$ (7 mL, 100 mmol) in $CHCl_3$ (150 mL) is heated at reflux for 3 h. The solvent and excess $SOCl_2$ are evaporated into a cold trap and the residue is redissolved in $CHCl_3$ (50 mL). The solution is added to a solution of methylbenzylamine (1.45 g, 12 mmol) and DIPEA (2 mL, 12 mmol) in cold (0°C) $CHCl_3$ (100 mL). The mixture is stirred for 15 h at r.t. and then quenched with sat. aq. Na_2CO_3 (50 mL). The phases are separated and the aq. phase is extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts are washed with 1N aq. HCl (50 mL) and sat. aq. NaCl (50 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, heptane-EtOAc) to provide the title compound.

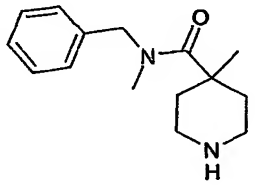
A12.3. 4-Phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.

A mixture of 4-(benzyl-methyl-carbamoyl)-4-phenyl-piperidine-1-carboxylic acid benzyl ester (4.4 g, 10 mmol) and Pd-C (10%, 400 mg) in MeOH (200 mL) is hydrogenated at r.t. and atmospheric pressure for 3 h. The mixture is filtered and evaporated. The resiudue is purified by reversed phase MPLC to provide the title compound.

The following intermediates are prepared from 4-phenyl-piperidine-1,4-dicarboxylic acid monobenzyl ester (Example A12.1) and commercially available amines using the method described in Example A12.

Example No	Example
A12.	4-Phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide
A13.	4-Phenyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide

A14. 4-Methyl-piperidine-4-carboxylic acid benzyl-methyl-amide.



A14.1. 4-Methyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester.

A solution of NaHMDS (2M in THF, 148 mmol, 74 mL, diluted to 100 mL) is cooled at -78°C and a solution of piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (25.74 g, 100 mmol) in THF (50 mL of solution) is added slowly. The mixture is stirred for 2 h at -78°C. Methyliodide (7.5 mL, 120 mmol) is dissolved in THF (60 mL) and the cold solution of enolate is added. The mixture is stirred at r.t. for 1 h and quenched with HCl (1M, 75 mL) and ether (200 mL). the phases are separated and the organic phase washed with HCl (1M, 2 x 50 mL) and NaOH (1M, 2 x 50 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated to provide the crude title compound.

A14.2. 4-Methyl-piperidine-1,4-dicarboxylic acid monobenzyl ester.

4-Methyl-piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester (2.71 g, 10 mmol) is heated with 6M aq. HCl (20 mL) at 95 °C for 2 days. The mixture is cooled, basified with 33% aq. NaOH (ice bath cooling) and extracted with ether (2 x 50 mL). A spatula of NaH2PO4 is added, then the pH adjusted to 7 with conc. aq. HCl, CH_2Cl_2 (50 Vol%) is added and the mixture cooled at 0°C. Carbonic acid benzyl ester 2,5-dioxo-pyrrolidin-1-yl ester (1.508 g, 5 mmol) is added to the strongly stirred biphasic system and the mixture is stirred for 2 h. The pH is adjusted to 14 with aq. NaOH (1M) and the phases are separated. The aq. phase is extracted with CH_2Cl_2 (2 x 50 mL), the organic extracts are discarded. The pH is

adjusted to 2 and the mixture is extracted with $CHCl_3$ (4 x 50 mL). The organic extracts are dried (Na_2SO_4), filtered and evaporated to provide the title compound.

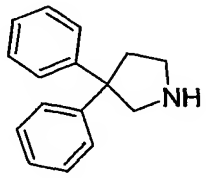
A14.3. 4-Methyl-piperidine-4-carboxylic acid benzyl-methyl-amide.

The compound is prepared from 4-methyl-piperidine-1,4-dicarboxylic acid monobenzyl ester and benzylmethylamine using the method described in Example A12.

The following intermediates are prepared from piperidine-1,4-dicarboxylic acid 1-tert-butyl ester 4-ethyl ester, commercially available alkyliodides and commercially available amines using the method described in Example A14.

Example No	Example
A14.	4-Methyl-piperidine-4-carboxylic acid benzyl-methyl-amide
A15.	4-Methyl-piperidine-4-carboxylic acid (4-methoxy-benzyl)-methyl-amide
A16.	4-Ethyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide
A17.	4-Ethyl-piperidine-4-carboxylic acid benzyl-methyl-amide

A18. 3,3-Diphenyl-pyrrolidine.



A suspension of $LiAlH_4$ (560 mg, 14.75 mmol) in THF (50 mL) is cooled at 0°C and a solution of 4-bromo-2,2-diphenylbutyronitrile (1.50 g, 5 mmol) in THF (20 mL) is slowly added. The mixture is stirred at r.t. for 15 h, carefully quenched with MeOH and $NaHCO_3$ and filtered. The filtrate is evaporated, the residue taken up in CH_2Cl_2 (100 mL) and washed with sat. aq. Na_2CO_3.(50 mL). The aq. phase is re-extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic extracts are dried

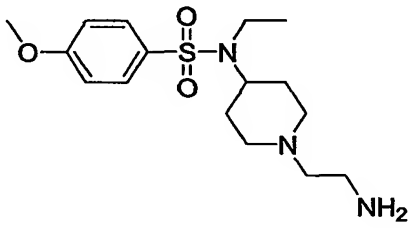
(Na_2SO_4), filtered and evaporated. The residue is purified by reversed phase MPLC to provide the title compound.

Preparation of Intermediates. Example B.

B1. 2-(4-Benzylpiperidino)-1-ethanamine.

The material is commercially available.

B2. *N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide.



B2.1. (2-Bromo-ethyl)-carbamic acid tert-butyl ester.

To 1 N aq. NaOH (200 mL) is added MeOH (400 mL) and the resulting solution is cooled at 20 °C. 2-Bromoethylamine hydrobromide (25.0 g, 122 mmol) is added in a single portion, followed by di-tert-butyl dicarbonate (26.6 g, 122 mmol). The reaction mixture is stirred for 2.5 h. The MeOH is removed on a rotary evaporator, and the aq. suspension is extracted with CH_2Cl_2 (2 x 175 mL). The combined organic extracts are extracted with 5% aq. citric acid (300 mL), dried ($MgSO_4$), filtered, and evaporated to provide the title compound.

B2.2. (2-{4-[Ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidin-1-yl}-ethyl)-carbamic acid tert-butyl ester.

A mixture of *N*-ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide (Example A4., 1.19 g, 4 mmol), (2-bromo-ethyl)-carbamic acid tert-butyl ester (1.12 g, 5.0 mmol) and DIPEA (650 mg, 5 mmol) in THF (30 mL) is heated at reflux for 15 h. The solution is poured into Et_2O (150 mL) and extracted with sat. aq. Na_2CO_3 (2 x

50 mL) and sat. aq. NaCl (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by reversed phase MPLC to provide the title compound.

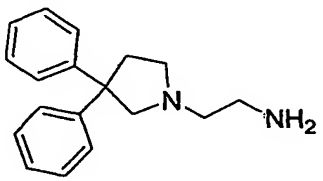
B2.3. *N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide.

The title compound is prepared from (2-{4-[ethyl-(4-methoxy-benzenesulfonyl)-amino]-piperidin-1-yl}-ethyl)-carbamic acid tert-butyl ester using the method described in Example A4.2.

The following intermediates are prepared from Examples A2. to A12. and (2-bromo-ethyl)-carbamic acid tert-butyl ester (Example B2.1.) using the method described in Example B2.

Example No	Example
B2.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-methoxy-benzenesulfonamide
B3	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-*N*-ethyl-4-fluoro-benzenesulfonamide
B4.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-4-bromo-*N*-ethyl-benzenesulfonamide
B5.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-4-methoxy-*N*-propyl-benzenesulfonamide
B6.	*N*-[1-(2-Amino-ethyl)-piperidin-4-yl]-4-fluoro-*N*-propyl-benzenesulfonamide
B7.	1-(2-Amino-ethyl)-4-benzyl-piperidin-4-ol
B8.	1-(2-Amino-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide

B9. 2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethylamine.



B9.1. (2-Bromo-ethyl)-carbamic acid benzyl ester.

2-Bromoethylamine hydrobromide (15 g, 73 mmol) and *N*-(benzyloxycarbonyloxy)-succinimide (15.5 g, 62 mmol) are suspended in CH_2Cl_2 (150 mL) at 0°C. TEA (9 mL, 65 mmol) is added slowly keeping the temperature at 0°C. After 1h the mixture is washed with 0.5M aq. $KHSO_4$ (50 mL) and sat. aq. NaCl (50 mL), the organic phase is dried (Na_2SO_4), filtered and evaporated to provide the title compound.

B9.2. [2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethyl]-carbamic acid benzyl ester.

(2-Bromo-ethyl)-carbamic acid benzyl ester (1.10 g, 4.26 mmol), 3,3-diphenyl-pyrrolidine (Example A18, 836 mg, 3.75 mmol) and DIPEA (1.0 mL 5.7 mmol) are dissolved in THF (20 mL) and stirred for 15 h at reflux. The mixture is quenched with Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

B9.3. 2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethylamine.

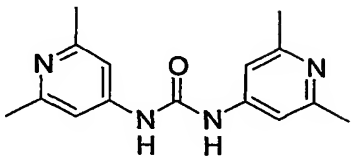
[2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethyl]-carbamic acid benzyl ester (1.44 g, 3.6 mmol) is dissolved in MeOH (50 mL) and Pd-C (10%, 150 mg) is added. The mixture is stirred under hydrogen atmosphere for 15 h. The mixture is filtered and the filtrate evaporated to provide the title compound.

The following intermediates are prepared from Examples A14. to A18 and (2-bromo-ethyl)-carbamic acid benzyl ester (Example B9.1.) using the method described in Example B9.

Example No	Example
B9.	2-(3,3-Diphenyl-pyrrolidin-1-yl)-ethylamine
B10.	1-(2-Amino-ethyl)-4-methyl-piperidine-4-carboxylic acid (4-methoxy-benzyl)-methyl-amide
B11.	1-(2-Amino-ethyl)-4-methyl-piperidine-4-carboxylic acid benzyl-methyl-amide

Preparation of Intermediates. Example C.

C1. 1,3-Bis-(2,6-dimethyl-pyridin-4-yl)-urea.



C1.1. 2,6-Dimethyl-4-nitro-pyridine 1-oxide.

Lutidine-*N*-oxide (19 g, 155 mmol) is cooled at 0°C and a mixture of fuming HNO_3 (100 %, 37.5 mL) and conc. H_2SO_4 (95-97%, 52.5 mL), prepared by addition of H_2SO_4 to HNO_3 at 0°C, is added slowly. The mixture is heated at 80°C for 3h. The cooled mixture is carefully poured into ice-water (500 mL). A white precipitate forms that is filtered. The precipitate is dissolved in CH_2Cl_2 (100 mL) and the filtrate is extracted with CH_2Cl_2 (4x 75 mL). The organic extracts are combined with the dissolved precipitate and washed with sat. aq. NaCl (2 x 75 mL), dried (Na_2SO_4), filtered and evaporated to provide the title compound.

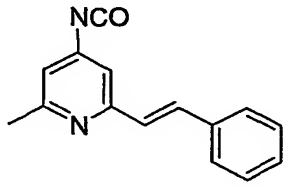
C1.2. 2,6-Dimethyl-pyridin-4-ylamine.

2,6-Dimethyl-4-nitro-pyridine 1-oxide (9.62 g, 57 mmol) is dissolved in AcOH (300 mL) and Fe (powder, 29 g) is added. The mixture is stirred for 1 h at 100°C. The mixture is cooled to r.t. and filtered. The filtercake is thoroughly washed with AcOH and then discarded. The filtrate is evaporated, diluted with water (100 mL), basified with NaOH (1 M, 100 mL), filtered from the formed precipitate and the filtrate is extracted with $CHCl_3$ (10 x 50 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated. The residue is crystallized from heptane-$CHCl_3$ to provide the title compound.

C1.3. 1,3-Bis-(2,6-dimethyl-pyridin-4-yl)-urea.

2,6-Dimethyl-pyridin-4-ylamine (1.22 g, 10 mmol) is dissolved in dry dioxane (30 mL) and CDI (891 mg, 5.5 mmol) is added. The mixture is heated at 80°C for 1 h. Further CDI (160 mg) is added and stirring is continued for 15 h. The mixture is evaporated and purified by FC (SiO_2, EtOAc-MeOH) to provide the title compound.

C2. 4-Isocyanato-2-methyl-6-(*E*)-styryl-pyridine.



C2.1. 2-Methyl-6-(*E*)-styryl-isonicotinic acid.

A suspension of 2-chloro-6-methyl-isonicotinic acid (171.6 mg, 1 mmol), (*E*)-2-phenyl-etheneboronic acid (180.0 mg, 1.2 mmol), K_2CO_3 (414 mg), $Pd(dppf)Cl_2$-CH_2Cl_2 (27 mg) in CH_3CN-H_2O (3:1, 10 mL) is stirred under argon at 90°C for 15 h. The solution is cooled to r.t. and aq. hydrochloric acid (2 M, 1.5 mL) is added to adjust the pH at 3. The mixture is evaporated to dryness and purified by reversed phase MPLC to provide the title compound.

C2.2. 2-Methyl-6-(*E*)-styryl-isonicotinoyl azide.

To a solution of 2-methyl-6-(*E*)-styryl-isonicotinic acid (214 mg, 0.89 mmol) in DMF (5 mL) is added at 0°C TEA (0.21 mL, 1.5 mmol) and slowly (30 min) DPPA (366 mg, 1.33 mmol). The reaction mixture is stirred for 0.5 h at 0°C and 0.5 h at r.t. The reaction is quenched with ice (20 g) and extracted with Et_2O (6 x 30 mL). The combined organic extracts are washed successively with saturated $NaHCO_3$ (2 x 15 mL) and water (2 x 10 mL), and are evaporated in vacuo without heating. The residue is purified by FC (SiO_2, EtOAc-heptane) to provide the title compound.

C2.3. 4-Isocyanato-2-methyl-6-(*E*)-styryl-pyridine.

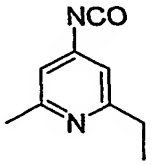
2-Methyl-6-(*E*)-styryl-isonicotinoyl azide (79.9 mg, 0.3 mmol) is dissolved in dry toluene (4 mL) and heated at reflux for 2h. The resulting solution of the title compound is carried forward without further isolation.

The following intermediates are prepared from 2-chloro-6-methyl-isonicotinic acid or 2-chloro-isonicotinic acid and commercially available boronic acids using the method described in Example C2.

Example No	Example

C2.	4-Isocyanato-2-methyl-6-(*E*)-styryl-pyridine
C3.	2-[(*E*)-2-(4-Fluoro-phenyl)-vinyl]-4-isocyanato-6-methyl-pyridine
C4.	4-Isocyanato-2-(*E*)-styryl-pyridine
C5.	2-[(*E*)-2-(4-Fluoro-phenyl)-vinyl]-4-isocyanato-pyridine
C6.	2-[(*E*)-2-(4-Chloro-phenyl)-vinyl]-4-isocyanato-pyridine

C7. 2-Ethyl-4-isocyanato-6-methyl-pyridine.



C7.1. 2-Chloro-6-methyl-isonicotinic acid tert-butyl ester.

N,*N*-dimethylformamide-di-*tert*.-butyl-acetal (19 mL, 80 mmol) is added during 40 min to a hot (65°C, flask temperature) suspension of 2-chloro-6-methyl-isonicotinic acid (3.40 g, 19.8 mmol) in dry toluene (100 mL). The clear orange solution is stirred at 80°C for 48 h, cooled to r.t. and diluted with toluene (100 mL). The solution is washed with water (2 x 40 mL), sat. aq. $NaHCO_3$ (3 x 30 mL) and sat. aq. NaCl (25 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC (SiO_2, CH_2Cl_2-MeOH) to provide the title compound.

C7.2. 2-Ethyl-6-methyl-isonicotinic acid.

A solution of ethylmagnesiumbromide (freshly prepared from ethylbromide (392 mg, 3.6 mmol) and magnesium (83 mg, 3.4 mmol)) in Et_2O (10 mL) is added to a cooled (-40°C) and mechanically stirred solution of 2-chloro-6-methyl-isonicotinic acid tert-butyl ester (0.76 g, 3.34 mmol), $Fe(acac)_3$ (21.2 mg, 0.06 mmol) and NMP (0.6 mL) in THF (60 mL). The mixture is warmed to r.t. during 0.5 h, diluted with Et_2O (150 mL) and quenched with aq. $KHSO_4$ (1 M, 40 mL). The phases are separated and the aq. phase is extracted with Et_2O (2 x 50 mL). The combined organic extracts are dried ($MgSO_4$), filtered and evaporated. The residue is purified by reversed phase MPLC. The obtained 2-ethyl-6-methyl-isonicotinic acid tert-butyl ester is dissolved in CH_2Cl_2 (10 mL). TFA (10 mL) is added and the mixture

stirred at r.t. for 0.5 h. The mixture is evaporated and the residue dried in HV to provide the title compound.

C7.3. 2-Ethyl-6-methyl-isonicotinoyl azide.

The title compound is prepared from 2-ethyl-6-methyl-isonicotinic acid using the method described in Example C2.2.

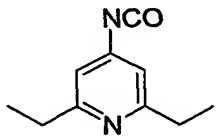
C7.4. 2-Ethyl-4-isocyanato-6-methyl-pyridine.

The title compound is prepared from 2-ethyl-6-methyl-isonicotinoyl azide using the method described in Example C2.3.

The following intermediates are prepared from 2-chloro-6-methyl-isonicotinic acid and commercially available alkylbromides using the method described in Example C7.

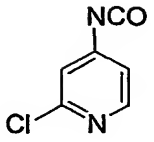
Example No	Example
C7.	2-Ethyl-4-isocyanato-6-methyl-pyridine
C8.	4-Isocyanato-2-methyl-6-phenethyl-pyridine
C9.	4-Isocyanato-2-methyl-6-propyl-pyridine

C10. 4-Isocyanato-2,6-diethyl-pyridine.



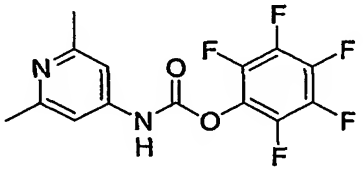
The title compound is prepared from 2,6-dichloro-isonicotinic acid tert-butyl ester (prepared from 2,6-dichloro-isonicotinic acid according to the method of Example C7.1) and 2.2 equivalents of ethylbromide using the methods described in Example C7.

C11. 2-Chloro-4-isocyanatopyridine.



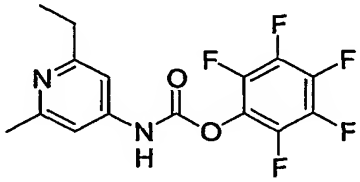
The title compound is prepared from commercially available 2-chloro-isonicotinic acid using the method described in Example C2.2. and C2.3.

C12. (2,6-Dimethyl-pyridin-4-yl)-carbamic acid pentafluorophenyl ester.



A solution of 2,6-dimethyl-pyridin-4-ylamine (Example C1.2., 1.23 g, 10 mmol) in THF (30 mL) is slowly added to a cooled (-10°C) solution of bis(pentafluorophenyl)carbonate (3.94 g, 10 mmol) in THF (10 mL). The mixture is stirred at r.t. for 48 h and the solution of title compound is used as stock solution for subsequent coupling reactions.

C13. (2-Ethyl-6-methyl-pyridin-4-yl)-carbamic acid pentafluorophenyl ester.



C13.1. 2-Ethyl-6-methyl-4-nitro-pyridine 1-oxide.

2-Ethyl-6-methylpyridine (22.2 g, 183 mmol) is dissolved in $CHCl_3$ (250 mL) and 3-chloroperbenzoic acid (49.7 g, 201.6 mmol) is added protionwise. The mixture is stirred for 15 h, filtered and evaportaed. The residue is dissolved in ether (250 mL) and washed with aq. NaOH (1M, 6 x 100 mL). The organic phase is dried (MgSO4), filtered and evaporated to provide the crude *N*-oxide.

The *N*-oxide is slowly added to a cooled (0°C) mixture of fuming HNO_3 (100 %, 40.6 mL) and conc. H_2SO_4 (95-97%, 55.4 mL), prepared by addition of H_2SO_4 to HNO_3 at 0°C. The mixture is heated at 80°C for 1h. The cooled mixture is carefully poured into ice-water (400 mL). The mixture is diluted with CH_2Cl_2 (100 mL), the phases separated and the aq. phase is extracted with CH_2Cl_2 (4x 75 mL). The organic extracts are washed with sat. aq. NaCl (2 x 75 mL), dried (Mg_2SO_4), filtered and evaporated to provide the title compound.

C13.2. 2-Ethyl-6-methyl-pyridin-4-ylamine.

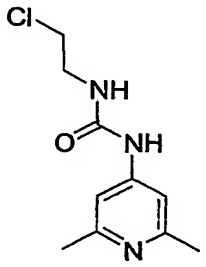
2-Ethyl-6-methyl-4-nitro-pyridine 1-oxide (27.65 g, 151.8 mmol) is dissolved in AcOH (330 mL) and Fe (powder, 33.9 g) is added. The mixture is stirred for 1 h at 100°C. The mixture is cooled to r.t. and filtered. The filtercake is thoroughly washed with AcOH and then discarded. The filtrate is evaporated, diluted with water (100 mL), basified (pH >10) with NaOH (1 M, 100 mL), filtered from the formed precipitate and the filtrate is extracted with CH_2Cl_2 (10 x 75 mL). The combined organic extracts are dried ($MgSO_4$), filtered and evaporated to provide the title compound.

C13.3. (2-Ethyl-6-methyl-pyridin-4-yl)-carbamic acid pentafluorophenyl ester.

A solution of 2-ethyl-6-methyl-pyridin-4-ylamine (1.33 g, 9.8 mmol) in THF (25 mL) is slowly added to a solution of bis(pentafluorophenyl)carbonate (3.99 g, 10.1 mmol) in THF (10 mL). The mixture is stirred at r.t. for 48 h and the solution of title compound is used as stock solution for subsequent coupling reactions.

Preparation of Intermediates. Example D.

D1. 1-(2-Chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea.

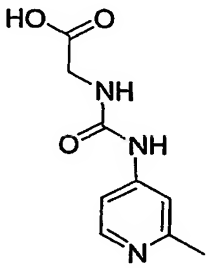


2,6-Dimethyl-pyridin-4-ylamine (Example C1.2., 1.22 g, 10 mmol) is dissolved in dry THF (30 mL) and 1-chloro-2-isocyanato-ethane (1.06 g, 10 mmol) is added. The mixture is stirred at r.t. for 15 h. The mixture is evaporated and the residue purified by MPLC to provide the title compound.

The following intermediates are prepared from 2,6-dimethyl-pyridin-4-ylamine or 2-ethyl-6-methyl-pyridin-4-ylamine (Example C13.2.) and 1-chloro-2-isocyanato-ethane using the method described in Example D1.

Example No	Example
D1.	1-(2-Chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea
D2.	1-(2-Chloro-ethyl)-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea

D3. [3-(2-Methyl-pyridin-4-yl)-ureido]-acetic acid.



D3.1. 2-Methyl-pyridin-4-ylamine.

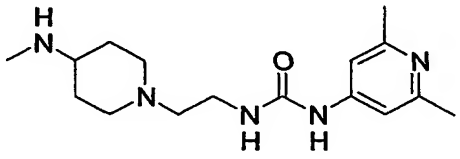
The material is prepared from commercially available 2-methyl-4-nitro-pyridine 1-oxide using the method described for Example C1.2.

D3.2. [3-(2-Methyl-pyridin-4-yl)-ureido]-acetic acid.

2-Methyl-pyridin-4-ylamine (1.08 g, 10 mmol) is dissolved in dry THF (30 mL) and isocyanatoacetic acid ethyl ester (1.29 g, 10 mmol) is added. The mixture is stirred at r.t. for 15 h. The mixture is evaporated and 6N aq. HCl (20 mL) is added. The mixture is stirred at 50°C for 6 h, evaporated and the residue purified by reversed phase MPLC to provide the title compound.

Preparation of Intermediates. Example E.

E1. 1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(4-methylamino-piperidin-1-yl)-ethyl]-urea.



Example E1.1. 4-(tert-Butoxycarbonyl-methyl-amino)-piperidine-1-carboxylic acid benzyl ester.

A mixture of commercially available 4-oxo-piperidine-1-carboxylic acid benzyl ester (4.67 g, 20 mmol) and methylamine (8 M in EtOH, 12.5 mL, 100 mmol) in dioxane (total volume of 100 mL) is stirred at r.t. for 15 min. $NaBHAc_3$ (6.4 g, 30 mmol) is added and the mixture is stirred for 15 h. The mixture is quenched with 1 M aq. NaOH (30 mL) and stirred at r.t. for 30 min. The mixture is diluted with water (50 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The organic extracts are dried (Na_2SO_4), filtered and evaporated. The residue is dissolved in ether (200 mL) and TEA (1.4 mL, 10 mmol) and, subsequently, a solution of di-tert.butyl-dicarbonat (3.82 g, 17.5 mmol) in ether (10 mL) are added. The mixture is stirred at r.t. for 15 h and quenched with 1 M aq. NaOH (30 mL). The phases are separated and the organic phase is washed with 1 M aq. NaOH (30 mL), 1 M aq. $KHSO_4$ (2 x 30 mL) and sat. aq. NaCl (30 mL). The organic phase is dried (Na_2SO_4), filtered and evaporated to provide the title compound.

Example E1.2. Methyl-piperidin-4-yl-carbamic acid tert-butyl ester.

A mixture of 4-(tert-butoxycarbonyl-methyl-amino)-piperidine-1-carboxylic acid benzyl ester (17.5 mmol) and Pd-C (10%, 500 mg) in MeOH (150 mL) hydrogenated at atm. pressure and r.t. for 15 h. The mixture is filtered and evaporated. The residue is dissolved in CH_2Cl_2 (100 mL) and 1 M aq. NaOH (50 mL) is added. The mixture is stirred for 6 h at r.t., then the phases are separated and the aq. phase is extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated to provide the title compound.

Example E1.3. (1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester.

A suspension of methyl-piperidin-4-yl-carbamic acid tert-butyl ester (3.57 g, 16.7 mmol), $NaHCO_3$ (6.7 g, 79 mmol), NaI (1.5 g, 10 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1, 2.14 g 9.4 mmol) in THF (30 mL) is stirred at 50°C for 14 days. The mixture is quenched with Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (5 x 50 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (30 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by FC to provide the title compound.

Example E1.4. 1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(4-methylamino-piperidin-1-yl)-ethyl]-urea.

The title compound is prepared from (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester using the method described in Example A4.2.

The following intermediates are prepared using the method described in Example E1. Piperidines are obtained according to the method of Example E1.1 by reductive amination of 4-oxo-piperidine-1-carboxylic acid benzyl ester with ethylamine (2M in THF) or cyclopropylamine. Coupling of the protected piperidine, prepared by the method of Example E1.2., with 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1) or 1-(2-chloro-ethyl)-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea (Example D2) is achieved according to the method of Example E1.3.

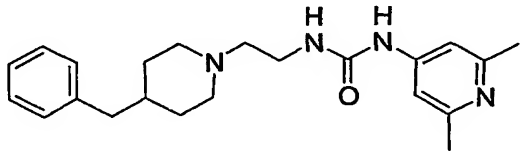
Deprotection according to the method of Example E1.4 provides the title compounds.

Example No	Example
E1.	1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(4-methylamino-piperidin-1-yl)-ethyl]-urea
E2.	1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(4-ethylamino-piperidin-1-yl)-ethyl]-urea
E3.	1-[2-(4-Cyclopropylamino-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea
E4.	1-[2-(4-Ethylamino-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea

PREPARATION OF FINAL PRODUCTS

Example 1.

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea.



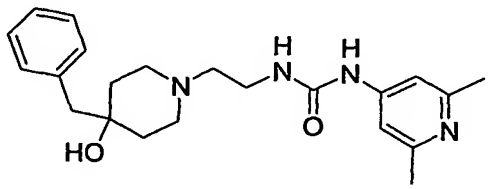
A suspension of 2-(4-benzylpiperidino)-1-ethanamine (Example B1, 54.6 mg, 0.25 mmol), TEA (35 µL, 0.25 mmol) and 1,3-bis-(2,6-dimethyl-pyridin-4-yl)-urea (Example B1, 67.6 mg 0.25 mmol) in dioxane (2 mL) is heated at reflux for 24h. The solvent is evaporated and the residue purified by HPLC to provide the title compound.

The following examples are pepared from intermediates Example B1.-B9. and Example C1. using the method described for Example 1.

Example No	Example	t_R	$[M+H]^+$
1	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea	0.63	367.42
2	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.70	500.47
3	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide	0.68	504.27
4	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide	0.68	492.23
5	1-(2,6-Dimethyl-pyridin-4-yl)-3-[2-(3,3-diphenyl-pyrrolidin-1-yl)-ethyl]-urea	0.68	415.20

Example 6.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea.

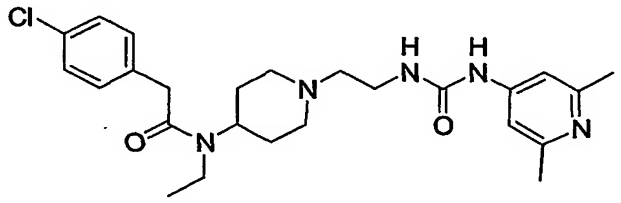


A suspension of commercially available 4-benzyl-piperidin-4-ol (383 mg, 2.0 mmol), $NaHCO_3$ (672 mg, 8.0 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1., 227.7 mg 1.0 mmol) in THF (4 mL) is stirred at 50°C for 4 days. The mixture is quenched with Na_2CO_3 (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (10 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
6	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea	0.55	383.37

Example 7.

2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide.



A suspension of 2-(4-chloro-phenyl)-*N*-ethyl-*N*-piperidin-4-yl-acetamide (Example A10., 3.37 g, 12.0 mmol), $NaHCO_3$ (5.4 g, 64 mmol), NaI (1.2 g, 8 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1, 1.82 g 8 mmol) in THF (40 mL) is stirred at 50°C for 27 days. The mixture is quenched with Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (70 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by MPLC to provide the title compound.

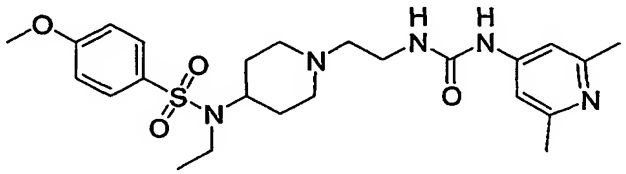
The following examples are prepared from intermediates Example A3.-A17. and intermediates Example D1. or D2. using the method described for Example 7.

Example No	Example	t_R	$[M+H]^+$
7	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide	0.67	472.41
8	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-benzenesulfonamide	0.67	490.27

9	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-(4-methoxy-phenyl)-acetamide	0.66	480.5
10	1-[2-(4-Benzyloxy-piperidin-1-yl)-ethyl]-3-(2,6-dimethyl-pyridin-4-yl)-urea	0.63	383.28
11	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide	0.67	530.38
12	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide	0.69	544.3
13	4-Ethyl-1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-(2-hydroxy-ethyl)-amide	0.63	496.42
14	4-Ethyl-1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidine-4-carboxylic acid benzyl-methyl-amide	0.67	466.36

Example 15.

***N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide.**



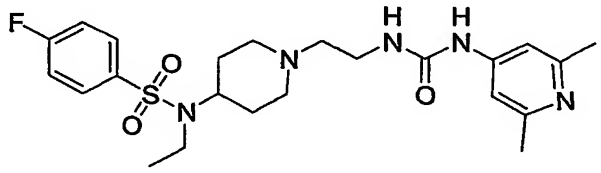
A suspension of *N*-ethyl-4-methoxy-*N*-piperidin-4-yl-benzenesulfonamide (Example A4., 2.09 g, 7.0 mmol), $NaHCO_3$ (3.4 g, 40 mmol), NaI (0.75 g, 5 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1, 1.14 g 5 mmol) in THF (30 mL) is stirred at 50°C for 27 days. The mixture is quenched with Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic

extracts are washed with sat. aq. Na_2CO_3 (70 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by MPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
15	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide	0.66	490.32

Example 16.

***N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide).**



A suspension of *N*-ethyl-4-fluoro-*N*-piperidin-4-yl-benzenesulfonamide (Example A5., 3.09 g, 10.8 mmol), $NaHCO_3$ (5.4 g, 64 mmol), NaI (1.2 g, 8 mmol) and 1-(2-chloro-ethyl)-3-(2,6-dimethyl-pyridin-4-yl)-urea (Example D1, 1.82 g 8 mmol) in THF (40 mL) is stirred at 50°C for 27 days. The mixture is quenched with Na_2CO_3 (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic extracts are washed with sat. aq. Na_2CO_3 (70 mL), dried (Na_2SO_4), filtered and evaporated. The residue is purified by MPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
16	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide	0.66	478.40

Example 17.

1-{2-{3-[2-Methyl-6-((E)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide.

To a solution of 1-(2-amino-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide (Example B8., 0.25 mmol) in CH_2Cl_2 is added a freshly prepared solution of 4-isocyanato-2-methyl-6-(*E*)-styryl-pyridine (Example C2., 0.3 mmol) in toluene (2 mL). The mixture is stirred for 15 h at 20 °C. Evaporation of the solvent and purification by HPLC provides the title compound.

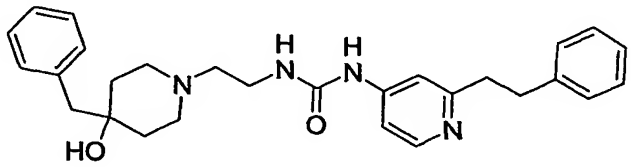
The following examples are pepared from Examples B1.-B8. and Examples C2.-C10. using the method described for Example 17.

Example No	Example	t_R	$[M+H]^+$
17	1-(2-{3-[2-Methyl-6-((*E*)-styryl)-pyridin-4-yl]-ureido}-ethyl)-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.79	588.46
18	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-6-methyl-pyridin-4-yl}-urea	0.76	473.42
19	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea	0.67	457.40
20	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-fluoro-phenyl)-vinyl]-pyridin-4-yl}-urea	0.69	475.40
21	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[(*E*)-2-(4-chloro-phenyl)-vinyl]-pyridin-4-yl}-urea	0.71	491.38
22	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.74	580.45

23	1-{2-[3-(2-Methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.74	528.5
24	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-6-propyl-pyridin-4-yl)-urea	0.70	395.55
25	*N*-Ethyl-4-methoxy-*N*-(1-{2-[3-(2-methyl-6-propyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.69	518.29
26	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea	0.66	381.27
27	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide	0.67	504.25
28	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.72	514.34
29	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-ethyl-6-methyl-pyridin-4-yl)-urea	0.58	397.21
30	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-benzenesulfonamide	0.66	492.20
31	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2,6-diethyl-pyridin-4-yl)-urea	0.66	395.24
32	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2,6-diethyl-pyridin-4-yl)-urea	0.60	411.21
33	*N*-(1-{2-[3-(2,6-Diethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzenesulfonamide	0.67	518.26
34	*N*-(1-{2-[3-(2,6-Diethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzenesulfonamide	0.67	506.24

Example 35.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea.



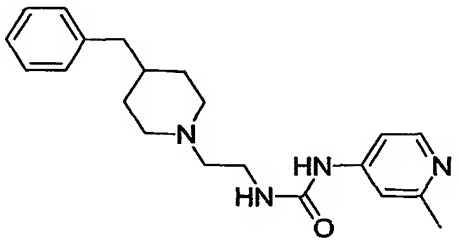
A suspension of 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-[2-((*E*)-styryl)-pyridin-4-yl]-urea (Example 19., 47.0 mg, 0.1 mmol) and Pd-C (10 %, 10 mg) in MeOH (10 mL) is stirred under hydrogen atmosphere for 15 h. The catalyst is filtered off and the reaction mixture evaporated to provide the title compound.

The following compounds are prepared from Examples 17.-20. using the method described for Example 35.

Example No	Example	t_R	$[M+H]^+$
35	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-phenethyl-pyridin-4-yl)-urea	0.67	459.41
36	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-pyridin-4-yl}-urea	0.68	477.44
37	1-{2-[3-(2-Methyl-6-phenethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.79	590.53
38	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-{2-[2-(4-fluoro-phenyl)-ethyl]-6-methyl-pyridin-4-yl}-urea	0.75	475.49

Example 39.

1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.



Example 39.1.

1-[2-(4-Benzyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.

To a cooled (0°C) mixture of [3-(2-methyl-pyridin-4-yl)-ureido]-acetic acid (Example D3., 105 mg, 0.5 mmol), 4-benzylpiperidine (Example A1., 105 mg, 0.6 mmol), HOBt (81 mg, 0.6 mmol), TEA (0.14 mL, 1 mmol) and a cat. amount of DMAP in CH_2Cl_2 (20 mL) are added, followed by EDC (115 mg, 0.6 mmol). The mixture is stirred at r.t. for 15 h. The mixture is quenched with sat. aq. Na_2CO_3 (25 mL), the phases are separated, and the aq. phase is extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts are dried (Na_2SO_4), filtered and evaporated to provide the crude title compound.

Example 39.2.

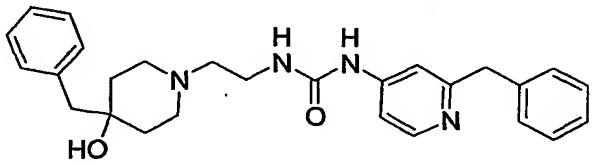
1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea.

The crude 1-[2-(4-benzyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2-methyl-pyridin-4-yl)-urea (Example 39.1., 0.5 mmol) is dissolved in THF (5 mL) and added to a cooled (0°C) suspension of $LiAlH_4$ (100 mg, 2.5 mmol) in THF (20 mL). The mixture is warmed during 15 h to r.t. The reaction mixture is carefully added to EtOAc (100 mL) and MeOH (5 mL), and, subsequently, sat. aq. $NaHCO_3$ (2 mL) are added. The mixture is filtered, the filtercake washed with MeOH (2 x 50 mL), and the filtrate is evaporated. The residue is taken up in a minimal amount of MeOH, diluted with CH_2Cl_2, dried (Na_2SO_4), filtered and evaporated. The residue is purified by HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
39	1-[2-(4-Benzyl-piperidin-1-yl)-ethyl]-3-(2-methyl-pyridin-4-yl)-urea	0.62	353.12

Example 40.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.



Example 40.1.

1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-chloro-pyridin-4-yl)-urea.

The title compound is prepared from 2-(4-benzylpiperidino)-1-ethanamine (Example B1.) and 2-chloro-4-isocyanatopyridine (Example C11.) using the method described in Example 17.

Example 40.2.

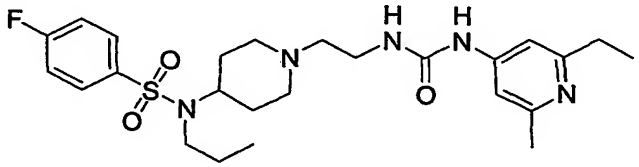
1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea.

A mixture of 1-[2-(4-benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-chloro-pyridin-4-yl)-urea (98 mg, 0.3 mmol), *B*-benzyl-9-BBN (0.5 M in THF, 4 mL, 2 mmol), triphenylphosphine (29 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (11 mg, 0.01 mmol), 2 M aq. K_2CO_3 (0.5 mL) and dimethoxyethane (1 mL) is degassed and heated under argon at 90°C for 7 days. The mixture is evaporated and the residue purified by preparative HPLC to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
40	1-[2-(4-Benzyl-4-hydroxy-piperidin-1-yl)-ethyl]-3-(2-benzyl-pyridin-4-yl)-urea	0.65	445.4

Example 41.

***N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide.**



To a solution of (2-ethyl-6-methyl-pyridin-4-yl)-carbamic acid pentafluorophenyl ester (Example C13., 0.2M, 3 mL, 0.6 mmol) is added a solution of *N*-[1-(2-amino-ethyl)-piperidin-4-yl]-4-fluoro-*N*-propyl-benzenesulfonamide (Example B6., 182 mg, 0.53 mmol). The mixture is stirred at r.t. for 15 h. The mixture is evaporated and the residue purified by HPLC to provide the title compound.

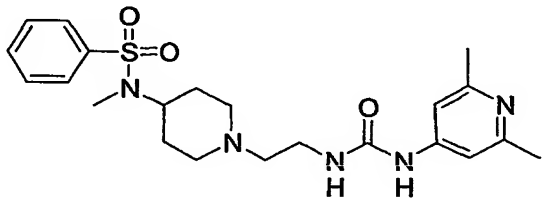
The following compounds are prepared from Examples B4.-B6. or B10.-B11. and Examples C13. or C14. using the method described for Example 41.

Example No	Example	t_R	$[M+H]^+$
41	*N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide	0.69	506.27
42	4-Bromo-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.7	554.2
43	*N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-propyl-benzenesulfonamide	0.69	518.23
44	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-methyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.65	452.35

45	1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-4-methyl-piperidine-4-carboxylic acid (4-methoxy-benzyl)-methyl-amide	0.65	482.32
46	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-methyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.63	438.22
47	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-methyl-piperidine-4-carboxylic acid (4-methoxy-benzyl)-methyl-amide	0.64	468.27

Example 48.

***N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide.**



To a cooled (0°C) mixture of 1-(2,6-dimethyl-pyridin-4-yl)-3-[2-(4-methylamino-piperidin-1-yl)-ethyl]-urea (Example E1., 0.3 mmol) and TEA (0.5 mL, 0.35 mmol) in CH_2Cl_2 (2 mL) is added a solution of benzenesulfonyl chloride (53.0 mg, 0.3 mmol) in CH_2Cl_2 (1 mL). The mixture is stirred at r.t. for 15 h and evaporated. the residue is purified by HPLC to provide the title compound.

The following compounds are prepared from Examples E1.–E4. using the method described for Example 48.

Example No	Example	t_R	$[M+H]^+$
48	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide	0.61	446.11

49	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-*N*-methyl-benzenesulfonamide	0.63	476.12
50	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methoxy-*N*-methyl-benzenesulfonamide	0.64	476.13
51	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,5-dimethoxy-*N*-methyl-benzenesulfonamide	0.64	506.15
52	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-dimethoxy-*N*-methyl-benzenesulfonamide	0.62	506.13
53	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4,*N*-dimethyl-benzenesulfonamide	0.64	490.12
54	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-methyl-benzenesulfonamide	0.63	464.09
55	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-fluoro-*N*-methyl-benzenesulfonamide	0.63	464.08
56	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-fluoro-*N*-methyl-benzenesulfonamide	0.62	464.08
57	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,4-difluoro-*N*-methyl-benzenesulfonamide	0.64	482.08
58	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-difluoro-*N*-methyl-benzenesulfonamide	0.66	482.07
59	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,6-difluoro-*N*-methyl-benzenesulfonamide	0.63	482.07

60	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-ethyl-*N*-methyl-benzenesulfonamide	0.68	474.13
61	*N*-{4-[(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-sulfamoyl]-phenyl}-acetamide	0.6	503.13
62	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-isopropoxy-*N*-methyl-benzenesulfonamide	0.69	504.16
63	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4,*N*-dimethyl-benzenesulfonamide	0.64	460.1
64	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,*N*-dimethyl-benzenesulfonamide	0.65	460.11
65	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,*N*-dimethyl-benzenesulfonamide	0.64	460.11
66	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-2,3,6,*N*-tetramethyl-benzenesulfonamide	0.71	518.16
67	4-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide	0.66	480.06
68	3-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide	0.66	480.05
69	2-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide	0.64	480.05
70	3,4-Dichloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-benzenesulfonamide	0.70	514.03

71	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-4-trifluoromethyl-benzenesulfonamide	0.70	514.11
72	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-3-trifluoromethyl-benzenesulfonamide	0.70	514.1
73	Thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.61	452.05
74	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.66	486
75	2,5-Dichloro-thiophene-3-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.68	519.99
76	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide	0.64	460.29
77	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-fluoro-benzenesulfonamide	0.66	478.11
78	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-fluoro-benzenesulfonamide	0.65	478.12
79	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,4-difluoro-benzenesulfonamide	0.67	496.14
80	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-difluoro-benzenesulfonamide	0.68	496.12
81	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,6-difluoro-benzenesulfonamide	0.65	496.13
82	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4,*N*-diethyl-benzenesulfonamide	0.7	488.15

83	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-isopropoxy-benzenesulfonamide	0.71	518.19
84	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methyl-benzenesulfonamide	0.67	474.14
85	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-methyl-benzenesulfonamide	0.67	474.13
86	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methyl-benzenesulfonamide	0.66	474.14
87	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-2,3,6-trimethyl-benzenesulfonamide	0.72	532.19
88	4-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide	0.68	494.11
89	3-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide	0.69	494.1
90	2-Chloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide	0.66	494.09
91	3,4-Dichloro-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzenesulfonamide	0.72	528.03
92	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-trifluoromethyl-benzenesulfonamide	0.71	528.1
93	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-trifluoromethyl-benzenesulfonamide	0.71	528.12

94	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-trifluoromethyl-benzenesulfonamide	0.69	528.11
95	Thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.63	466.08
96	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.69	500.07
97	2,5-Dichloro-thiophene-3-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.71	533.98
98	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2,5-dimethoxy-benzenesulfonamide	0.65	520.28
99	5-Bromo-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide	0.69	568.2
100	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-4-methyl-benzenesulfonamide	0.67	504.28
101	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-dimethoxy-benzenesulfonamide	0.65	520.29
102	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3-methoxy-benzenesulfonamide	0.67	490.27
103	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.65	472.16
104	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-fluoro-benzenesulfonamide	0.67	490.15

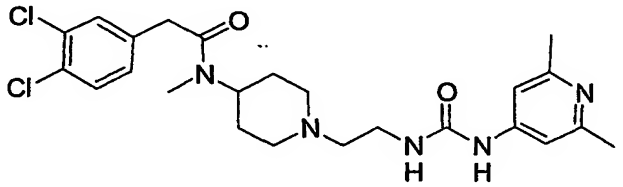
105	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-fluoro-benzenesulfonamide	0.65	490.11
106	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,4-difluoro-benzenesulfonamide	0.67	508.12
107	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-difluoro-benzenesulfonamide	0.69	508.11
108	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,6-difluoro-benzenesulfonamide	0.66	508.13
109	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-ethyl-benzenesulfonamide	0.71	500.17
110	*N*-(4-[Cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-sulfamoyl]-phenyl}-acetamide	0.63	529.05
111	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-isopropoxy-benzenesulfonamide	0.71	530.15
112	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methyl-benzenesulfonamide	0.68	486.1
113	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methyl-benzenesulfonamide	0.68	486.13
114	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methyl-benzenesulfonamide	0.67	486.09
115	4-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.69	506.11

116	3-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.69	506.08
117	2-Chloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.67	506.1
118	3,4-Dichloro-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-benzenesulfonamide	0.73	540.03
119	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-trifluoromethyl-benzenesulfonamide	0.72	540.12
120	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-trifluoromethyl-benzenesulfonamide	0.72	540.04
121	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-trifluoromethyl-benzenesulfonamide	0.7	540.07
122	Thiophene-2-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.64	478.06
123	5-Chloro-thiophene-2-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.7	512.05
124	2,5-Dichloro-thiophene-3-sulfonic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.71	545.94
125	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-methoxy-benzenesulfonamide	0.66	502.29
126	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methoxy-benzenesulfonamide	0.67	502.27

127	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2,5-dimethoxy-benzenesulfonamide	0.67	532.25
128	*N*-Cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4-methyl-benzenesulfonamide	0.67	516.3
129	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-methoxy-4-methyl-benzenesulfonamide	0.68	518.27
130	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3,4-dimethoxy-benzenesulfonamide	0.66	534.25
131	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-3-methoxy-benzenesulfonamide	0.68	504.27

Example 132.

2-(3,4-Dichloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide.



To a cooled (0°C) mixture of 1-(2,6-dimethyl-pyridin-4-yl)-3-[2-(4-methylamino-piperidin-1-yl)-ethyl]-urea (Example E1., 0.3 mmol) and TEA (0.5 mL, 0.35 mmol) in CH_2Cl_2 (2 mL) is added a solution of (3,4-dichloro-phenyl)-acetyl chloride (67.0 mg, 0.3 mmol) in CH_2Cl_2 (1 mL). The mixture is stirred at r.t. for 15 h and evaporated. the residue is purified by HPLC to provide the title compound.

The following compounds are prepared from Examples E1.–E4. using the method described for Example 132.

Example No	Example	t_R	$[M+H]^+$
132	2-(3,4-Dichloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide	0.69	495.24
133	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-(2-methoxy-phenyl)-*N*-methyl-acetamide	0.63	454.26
134	1-Phenyl-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.63	450.23
135	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.68	484.26
136	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.64	480.31
137	2-(3,4-Dimethoxy-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide	0.6	484.36
138	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide	0.66	458.23
139	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-(4-fluoro-phenyl)-*N*-methyl-acetamide	0.63	442.22
140	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-2-phenyl-acetamide	0.61	424.26
141	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-2-pyridin-2-yl-acetamide	0.47	425.23

142	2-(3-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide	0.66	458.24
143	2-(2-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-methyl-acetamide	0.64	458.21
144	2-(4-Chloro-phenyl)-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-isobutyramide	0.69	514.36
145	2-(2-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide	0.67	472.31
146	2-(3,4-Dichloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide	0.71	506.2
147	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(2-methoxy-phenyl)-acetamide	0.65	468.31
148	2-(4-Chloro-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-isobutyramide	0.7	500.31
149	1-Phenyl-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.64	464.31
150	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.68	498.3
151	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.65	494.34
152	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-phenyl-acetamide	0.62	438.27

153	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(4-methoxy-phenyl)-acetamide	0.62	468.31
154	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-methoxy-benzamide	0.6	454.26
155	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-3,4-dimethoxy-benzamide	0.59	454.26
156	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-4-fluoro-benzamide	0.6	442.24
157	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(3-methoxy-phenyl)-acetamide	0.62	468.34
158	2-(3,4-Dimethoxy-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide	0.61	498.38
159	2-(2,5-Dimethoxy-phenyl)-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-acetamide	0.64	498.32
160	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-thiophen-2-yl-acetamide	0.6	444.23
161	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-(4-fluoro-phenyl)-acetamide	0.63	456.3
162	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-benzamide	0.58	424.23
163	1-Phenyl-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.66	478.36
164	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.7	512.27

165	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid ethyl-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.67	508.32
166	*N*-Ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide	0.64	452.3
167	2-(4-Chloro-phenyl)-*N*-ethyl-*N*-(1-{2-[3-(2-ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide	0.69	486.31
168	2-(4-Chloro-phenyl)-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-isobutyramide	0.69	512.4
169	1-(4-Methoxy-phenyl)-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.67	506.35
170	2-(4-Chloro-phenyl)-*N*-cyclopropyl-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-acetamide	0.69	484.32
171	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.7	510.31
172	1-Phenyl-cyclopropanecarboxylic acid cyclopropyl-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-amide	0.66	476.41

Example 173.

***N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide.**

A suspension of 5-bromo-*N*-(1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide (Example 99, 30 mg, 0.05 mmol) and Pd-C (10 %, 20 mg) in MeOH (10 mL) is stirred under hydrogen

atmosphere for 15 h. The catalyst is filtered off and the reaction mixture evaporated to provide the title compound.

Example No	Example	t_R	$[M+H]^+$
173	*N*-(1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-*N*-ethyl-2-methoxy-benzenesulfonamide	0.64	490.13

EXAMPLE 174. IN VITRO BIOLOGICAL CHARACTERIZATION

The inhibitory activity of the compounds of General Formula 1 on the actions of urotensin II can be demonstrated using the test procedures described hereinafter:

1) INHIBITION OF HUMAN [^{125}I]-UROTENSIN II BINDING TO A RHABDOMYOSARCOMA CELL LINE

Whole cell binding of human [^{125}I]-urotensin II is performed using human-derived TE-671 rhabdomyosarcoma cells (Deutsche Sammlung von Mikroorganismen und Zellkulturen, cell line #ACC-263), by methods adapted from a whole cell endothelin binding assay (Breu V et al, In vitro characterization of Ro-46-2005, a novel synthetic non-peptide antagonist of ET_A and ET_B receptors. FEBS Lett. 1993, 334, 210-214).

The assay is performed in 250 µL Dulbecco's Modified Eagle Medium, pH 7.4 (GIBCO BRL, CatNo 31885-023), including 25 mM HEPES (Fluka, CatNo 05473), 1.0 % DMSO (Fluka, CatNo 41644) and 0.5% (w/v) BSA Fraction V (Fluka, CatNo 05473) in polypropylene microtiter plates (Nunc, CatNo 442587). 300'000 suspended cells are incubated with gentle shaking for 4 h at 20°C with 20 pM human [^{125}I]Urotensin II (Anawa Trading SA, Wangen, Switzerland, 2130Ci/mmol) and increasing concentrations of unlabeled antagonist. Minimum and maximum binding are derived from samples with and without 100 nM unlabelled U-II, respectively. After the 4 h incubation period, the cells are filtered onto GF/C filterplates (Packard, CatNo 6005174). The filter plates are dried, and then 50 µL scintillation cocktail (Packard, MicroScint 20, CatNo 6013621) is added to each

well. The filterplates are counted in a microplate counter (Packard Bioscience, TopCount NXT).

All test compounds are dissolved and diluted in 100% DMSO. A ten-fold dilution into assay buffer is performed prior to addition to the assay. The final concentration of DMSO in the assay is 1.0%, which is found not to interfere with the binding. IC50 values are defined as the concentration of antagonist inhibiting 50% of the specific binding of [^{125}I]human U-II. Specific binding is the difference between maximum binding and minimum binding, as described above. An IC_{50} value of 0.206 nM is found for unlabeled human U-II. The compounds of the invention are found to have IC_{50} values ranging from 0.1 to 1000 nM in this assay.

2) INHIBITION OF HUMAN [^{125}I]-UROTENSIN II BINDING TO MEMBRANES FROM RECOMBINANT CELLS CARRYING THE UROTENSIN II-RECEPTOR

Membranes from CHO cells expressing human Urotensin II receptor were prepared as described before (Breu V. et al, FEBS Lett 1993; 334:210-214; Martine Clozel et. al., "Pharmacology of the Urotensin-II Receptor Antagonist ACT-058362: First Demonstration of a Pathophysiological Role of the Urotensin System", J Pharmacol Exp Ther: 2004; DOI:10.1124/jpet.104.068320; WO-1999/40192). The binding assay was performed in 200 µl of PBS 1x pH 7.4 including 1 mM EDTA, 2.5% DMSO and 0.5% (w/v) BSA in polypropylene microtiter plates. Membranes containing 2-5 µg protein were incubated for 4 hours at room temperature with 20 pM (12000 cpm) [^{125}I]-Urotensin II and increasing concentrations of unlabeled antagonists. Minimum and maximum binding were derived from samples with and without 1 µM of unlabeled Urotensin II, respectively. After 4 hours of incubation, the membranes were filtered onto filterplates and washed 3 times with PBS 1x, 0.1% (w/v) BSA. 25 µl of scintillation cocktail was added to each well after drying the plates and the radioactivity on the filterplates was determined in a microplate counter.

The compounds of General Formula 1 are found to have IC_{50} values ranging from 0.1 to 1000 nM in this assay. Preferred compounds of General Formula 1 have IC_{50} values ranging from 0.1 to 100 nM. Most preferred compounds of General Formula 1 have IC_{50} values ranging from 0.1 to 10 nM.

In the following table IC_{50} values of compounds of General Formula 1 are summarized.

Example No	Example	IC_{50} [nM]
2	1-{2-[3-(2,6-Dimethyl-pyridin-4-yl)-ureido]-ethyl}-4-phenyl-piperidine-4-carboxylic acid benzyl-methyl-amide	0.7
41	*N*-(1-{2-[3-(2-Ethyl-6-methyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-4-fluoro-*N*-propyl-benzenesulfonamide	0.4
74	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-methyl-amide	0.5
96	5-Chloro-thiophene-2-sulfonic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.2
150	1-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (1-{2-[3-(2,6-dimethyl-pyridin-4-yl)-ureido]-ethyl}-piperidin-4-yl)-ethyl-amide	0.7

3) INHIBITION OF HUMAN UROTENSIN II-INDUCED CONTRACTIONS ON ISOLATED RAT THORACIC AORTA :

Adult male rats (Wistar or Sprague-Dawley) are euthanized by CO_2. An aortic segment (12mm) is isolated immediately distal to the left sub-clavian arterial branch, and vessel rings (3mm wide) are prepared. The endothelium is removed by inserting the tip of a watchmaker's forceps inside the lumen and gently rolling the tissue on a moist filter paper. Aortic rings are suspended in tissue baths (10 mL) containing Krebs-Henseleit buffer of the following composition (mM): NaCl 115; KCl 4.7; $MgSO_4$ 1.2; KH_2PO_4 1.5; $CaCl_2$ 2.5; $NaHCO_3$ 25; glucose 10. Bathing solution is maintained at 37°C and aerated with 95%O_2/ 5%CO_2 (pH 7.4). A resting force of 2 g (19.6 mN) is applied to the vessel, and changes in force generation are recorded using an EMKA automated system (EMKA Technologies

SA, Paris, France). The viability of each aortic ring is determined by contraction to a depolarising concentration of KCl (60 mM). After washout, the successful removal of endothelium is tested by the failure of acetylcholine (10 μM) to relax vessels constricted with phenylephrine (1 μM). Following further washout, tissues are exposed to either drug vehicle (control) or test compound for 20 minutes. A cumulative concentration-response curve to h-UII (30 pM-0.3 μM) is then obtained. Contraction of vessels to h-UII is expressed as a percentage of the initial contraction to KCl (60 mM). If the test compound displays competitive antagonism (causes parallel right-ward displacement of concentration-effect curve without diminishing the maximum response), then the inhibitory potency is quantified by calculation of the pA_2 value for the test compound (pA_2 value is the negative logarithm of the theoretical antagonist concentration which induces a two-fold shift in the EC_{50} value for h-U-II).